FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE (GIDAC)

Wednesday, January 12, 2011

8:00 a.m. to 4:00 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

Ronald Fogel, M.D.
Principal
Digestive Health Center of Michigan
Chesterfield, MI

William Hasler, M.D.
Professor of Internal Medicine
University of Michigan Health System
Division of Gastroenterology
Ann Arbor, MI

Jean-Pierre Raufman, M.D. (Chair)
Head, Division of Gastroenterology/Hepatology
Professor of Medicine
University of Maryland School of Medicine
Baltimore, MD

Jill Sklar (Consumer Representative)
Publications Coordinator
Beaumont Hospitals
Royal Oak, MI

TEMPORARY VOTING MEMBERS

Christopher Forsmark, M.D.
Professor of Medicine
Chief, Division of Gastroenterology,
Hepatology, and Nutrition
University of Florida
Gainesville, FL

Charles Hawkins (Patient Representative)
Baltimore, MD

Jesse Joad, M.D., M.S.
Professor and Associate Dean Diversity and
Faculty Life Emeritus
University of California, Davis
Davis, CA

Alexander Krist, M.D., M.P.H.
Associate Professor
Department of Family Medicine
Virginia Commonwealth University
Richmond, VA

Jenifer Lightdale, M.D.
Assistant Professor in Pediatrics
Gastroenterology and Nutrition
Children's Hospital Boston
Boston, MA

Mark Lowe, M.D., Ph.D.
Professor of Pediatrics
University of Pittsburgh
University of Pittsburgh Medical Center (UPMC)
Pediatrics/Gastroenterology
Hepatology and Nutrition
Pittsburgh, PA

Weichung Shih, Ph.D.
Professor and Chair
Department of Biostatistics
University of Medicine and Dentistry of New Jersey
School of Public Health
Piscataway, NJ

TEMPORARY MEMBER (Non-Voting)

Richard Hubbard, M.D.
(Acting Industry Representative)
Senior Director, External Medical Affairs,
International
Office of the Chief Medical Officer
Pfizer, Inc.
New York, NY

REGULAR GOVERNMENT EMPLOYEE TEMPORARY MEMBER

(Voting)

Van Hubbard, M.D., Ph.D.
Assistant Surgeon General
Director, NIH Division of Nutrition
Research Coordination
National Institutes of Health
Department of Health and Human Services
Bethesda, MD

FDA (Non-Voting)

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Office of New Drugs
CDER, FDA

Gilbert Burckart, Pharm.D.
Associate Director for Regulatory Policy
Office of Clinical Pharmacology, Office of
Translational Sciences
CDER, FDA

Marjorie Dannis, M.D.
Medical Officer
Division of Gastroenterology Products
CDER, FDA

Andrew Mulberg, M.D., FAAP
Deputy Director
Division of Gastroenterology Products
CDER, FDA

Anil Rajpal, M.D.
Medical Team Leader
Division of Gastroenterology Products
CDER, FDA

I N D E X

I N D E X (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order and Introduction of Committee

DR. RAUFMAN: Good morning. I'd like to call to order this meeting of the Gastrointestinal Drugs Advisory Committee. My name is Jean-Pierre Raufman. I'm head of the Division of Gastroenterology and Hepatology at the University of Maryland-Baltimore and chair of this committee. And we'll move with introductions, starting with Dr. Richard Hubbard.

DR. R. HUBBARD: Yes. I'm Richard Hubbard. I'm from Pfizer. I'm the industry representative. I'm a senior director in the chief medical office, and I have about 15 years' experience in drug development in multiple therapeutic areas.

DR. KRIST: My name is Alex Krist. I'm an associate professor in the Department of Family Medicine at Virginia Commonwealth University.

DR. LIGHTDALE: My name is Jenifer Lightdale. I'm a pediatric gastroenterologist at Children's Hospital-Boston.

DR. FOGEL: My name is Ron Fogel. I'm a gastroenterologist in private practice in metropolitan Detroit.

DR. FORSMARK: I'm Chris Forsmark. I'm the chief of the Division of Gastroenterology at the University of Florida in Gainesville.

DR. LOWE: I'm Mark Lowe. I'm a pediatric gastroenterologist at Children's Hospital of Pittsburg.

MR. HAWKINS: I'm Charles Hawkins. I'm here as a patient representative. I have cystic fibrosis.

DR. SHIH: I'm Weichung Joe Shih, professor and chair of the Department of Biostatistics, University of Medicine and Dentistry, New Jersey School of Public Health.

DR. KHUC: Kristine Khuc, Designated Federal Official.

DR. JOAD: I'm Jesse Joad, Professor Emeritus, University of California at Davis. I'm a pediatric pulmonologist and did cystic fibrosis throughout my career.

MS. SKLAR: Jill Sklar, consumer representative.

DR. V. HUBBARD: I'm Van Hubbard. I'm the director of the NIH Division of Nutrition Research Coordination and associate director for Nutritional Sciences, NIDDK at NIH, and I'm a pediatrician by training and have worked with CF in the past.

DR. HASLER: I'm Bill Hasler, professor in the Division of Gastroenterology, University of Michigan.

DR. RAJPAL: I'm Anil Rajpal, medical team leader, Division of Gastroenterology Products, FDA.

DR. BURKHART: Gilbert Burkhart, associate director, Office of Clinical Pharmacology, CDER.

DR. MULBERG: Good morning. Andrew Mulberg, Division Deputy Director, Division of Gastroenterology Products, FDA.

DR. BEITZ: I'm Julie Beitz, Director, Office of Drug Evaluation III.

DR. RAUFMAN: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of

opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

I would like to remind everyone to please silence your cell phones and other electronic devices, if you have not already done so. The

committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Conflict of Interest Statement

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Gastrointestinal Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by, but not limited to, those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Federal Food, Drug, and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, the members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of

their spouses and minor children, and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of the safety and efficacy of New Drug Application 022486 for Sollpura, liprotamase, capsules by Alnara Pharmaceuticals for the proposed indication, use, in the treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, surgical removal of all part of the pancreas, or other conditions that may impair or limit function of the pancreas.

The pancreas is an organ involved, in part, in the digestion of food through the use of specialized proteins called enzymes. Exocrine pancreatic insufficiency is a decreased ability to digest food due to deficient enzyme production by the pancreas.

This is a particular matters meeting during

which specific matters related to Sollpura, liprotamase, will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection to this meeting. To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Richard Hubbard is serving as a nonvoting industry representative acting on behalf of regulated industry. Dr. Hubbard's role at this meeting is to present industry in general and not any particular company. Dr. Hubbard is currently an employee of Pfizer, Inc.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a

personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. RAUFMAN: Dr. Dannis, you just joined us. Could you please introduce yourself?

DR. DANNIS: Marjorie Dannis, a medical reviewer for DGP.

DR. RAUFMAN: Thank you. We'll now proceed with the FDA opening remarks.

Opening Remarks/Introduction/Background

DR. MULBERG: Good morning. On behalf of Donna Griebel, Director of the Division of Gastroenterology Products, Dr. Raufman, chair of the GI Drug Advisory Committee, I welcome the GIDAC members, my FDA colleagues, Alnara Pharmaceuticals, and other attendees to today's discussion.

This audience understands and is aware that

cystic fibrosis is a common autosomal recessive disease, affecting predominantly Caucasian Americans, but affects most racial groups. It has proteome manifestations particularly targeting the pancreas, gastrointestinal tract, liver, and lung.

Pancreatic insufficiency is classified in either a sufficient or insufficient status, and the work of Durie and colleagues, in some of the work, has related the genotype specifically of cystic fibrosis to understanding some elements of this pathology.

It's clear from this slide, from the CF Registry 2008, that survival has been impacted greatly due to a number of factors, including the close monitoring of patients by physicians, advent of new therapies, and the integration of nutritional management particularly in the care plans for CF patients managing pancreatic insufficiency. But it's also clear that, as reflected on the CF registry demonstrating growth as measured by the body mass index percentile, the CF goal of reaching patients to be at least 50th

percentile has yet to be reached; and that with the issues of age, it's clear that despite the marked advances in therapies, the goal of reaching this percentile of 50 percent has yet to be reached. The causes of this reflect the complex pathobiology underlying cystic fibrosis.

But it's clear that the therapeutic developments that have been brought to this community have markedly affected the survival of CF patients. Most notably, the work initially by Crozier in Toronto in the '70s demonstrated the criticality of the management of pancreatic enzyme replacement therapy. These data were supplemented by an important study by Corey and colleagues from Toronto in the '80s that strengthened the evidence that pancreatic enzymes had a favorable impact both on lung function and survival. These data have resulted in the integration of pancreatic enzyme products into the care plan for every cystic fibrosis patient.

But what is clear is that malnutrition still does exist globally. The issues that affect both

the U.S. are also replicated in other parts of the world, particularly in central Europe, Macedonia, Russia and Ukraine, in which the availability of pancreatic enzyme products is markedly limited.

In addition, as we have learned, as several of us attended a very important conference in 2005 on the confounding issues affecting both the pathobiology of efficacy, of understanding pancreatic enzyme products' efficacy in cystic fibrosis, understanding the roles of hepatobiliary and gastric interact factors, it's very clear that at least in cystic fibrosis, there are very many factors that would contribute to the efficacy of pancreatic enzyme products.

Some of those are listed here, including the roles of gastric emptying, both in CF patients, as well as what has been reported in adults with chronic pancreatitis; the role of gastric hyperacidity; the differences between children and adults; the role of small bowel overgrowth both as a primary effect of dysmotility, as well as a secondary effect; increased intestinal

permeability; the well documented bile acid malabsorption; and, importantly, the role of intraluminal factors that do affect pancreatic enzyme product availability, including mucus hypersecretion.

But it is known to date that in clinical trials performed for the approval of porcine-derived pancreatic enzyme products, there has not been the requirement for clinical outcome studies. The magnitude of change in the coefficient of fat absorption, referred to as CFA in this talk, required to achieve improvement of clinical outcome has not been definitively established.

In the trials that are performed to date, porcine PEPs have been shown to result in a 26 to 41 percent change in CFA and 47 to 61 percent in the subgroup of CF patients whose baseline CFA was less than 40 percent.

CFA has been accepted as a surrogate endpoint for PEPS, based on their history of efficacy and safety of use and decades of literature demonstrating the relationship of

malnutrition secondary to factors including pancreatic insufficiency and the relationships to growth/survival.

If a threshold exists for CFA to serve as a surrogate, approval of a product associated with a treatment effect that does not reach that threshold could result theoretically in weight loss, impaired growth, and detrimental effects on lung function.

In light of the limitations of the submitted studies and the absence of definitive information to establish the minimum magnitude of change of CFA that is necessary to achieve clinical benefit, we look forward today to the discussions raised in the following questions to the GI Advisory Committee.

Question 1. In the overall 726 population, is the observed difference in the change in CFA between the liprotamase group, 11 percent, and the placebo group, .2 percent, of sufficient magnitude to be clinically meaningful?

In the subgroup of patients with a baseline CFA less than 40 percent in Study 726, is the observed difference in patients less than 40

percent clinically meaningful?

Do the results of Study 726 and the exploratory analyses of data from 767, including comparisons to the CF registry data, constitute substantial evidence of the efficacy of liprotamase for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis, due to CF in children less than 7 years of age, and due to CF in children greater than 7 years of age?

Question 3. For each of the approved porcine-derived PEPs, a short-term trial in patients with EPI due to CF supported an approved indication of EPI due to CF or, in quotations, "or other conditions," based on a large body of evidence in the literature. However, liprotamase is a new drug that differs from the porcine-derived PEPs, and the majority of patients studied in this application were CF patients.

If you believe yes, do the data in the application support an indication for EPI due to conditions other than CF; for example, chronic pancreatitis or pancreatectomy?

Are there additional efficacy studies that should be obtained prior to approving liprotamase? If yes, please describe the design of these studies.

Are there safety concerns associated with the use of liprotamase in EPI, for example, distal intestinal obstruction syndrome, fibrosing colonopathy or other, that would preclude approval?

Are there additional safety data or studies that should be obtained prior to approving liprotamase for exocrine pancreatic insufficiency?

Based on currently available data, do the benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI? If yes, specify your answer, whether it is limited to a particular subpopulation either by age or etiology of exocrine pancreatic insufficiency.

Lastly, if you believe this product should be approved, are there any additional studies you would recommend post-approval?

Thank you.

DR. RAUFMAN: Thank you. Both the Food and

Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's

presentation.

Alnara Presentation - Don Burstyn

DR. BURSTYN: Good morning. My name is Don Burstyn. I'm Alnara's Senior Vice President of Regulatory Affairs. And on behalf of the employees of Alnara Pharmaceuticals and our corporate parent, Eli Lilly and Company, I'd like to thank the panel for meeting with us this morning to discuss Sollpura, which has a USAN name of liprotamase.

The agenda for today's sponsor's presentations is displayed on the screen. You have it in your handout, so I won't go into it in any detail.

The presentations will provide background information on liprotamase, exocrine pancreatic insufficiency, and the management of patients. The liprotamase efficacy and safety data will be presented, and the sponsor's presentations will conclude with comments regarding the overall benefit-risk profile.

Now, in addition to our speakers, joining us today are several experts. And we have Dr. Peter

Durie from the University of Toronto, Dr. Paul Watkins from the University of North Carolina at Chapel Hill; and, we have two statistical consultants, Dr. John Balser from Veristat and Marilyn Campion, an independent statistical consultant.

So we are here today to discuss liprotamase, proposed for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions.

Now, liprotamase is a new molecular entity. Its purpose is to digest foods into their absorbable constituents within the GI tract; so triglycerides into free fatty acids, proteins into small peptides and amino acids, and complex carbohydrates into simple sugars. And please note that the intact enzymes themselves are not absorbed.

Shown is an overview of the recommended dosing, and Dr. Brettman, in his presentation, will provide additional details on this. So for adults

and children 7 years and older, therapy with liprotamase starts with a single capsule with each meal or snack. For children 2 to 6 years of age, the capsule contents are suspended in 5 milliliters of water or apple juice and administered by units per gram of food, which translates to about 2.5 to 3.5 mls per child. The suspension can be taken as is or first added to soft acidic foods, such as applesauce or yogurt.

For all patients, the dose can be individualized. However, the maximum daily dose should not exceed the cystic fibrosis guidelines, Cystic Fibrosis Foundation guidelines, as shown on the slide. And these guidelines were initially established for the porcine products.

Shown is a much abbreviated historical overview of liprotamase, which I will abbreviate even further. In 2001, the Cystic Fibrosis Foundation provided their initial grant to support development of the product. Now, for us, importantly, in 2004, liprotamase was accepted into the FDA's Continuous Market Application Pilot 2

program. And the Pilot 2 program was an exploratory one that evaluated the impact of frequent scientific feedback with applicants during the IND phase on the quality of the development program and ultimately on the NDA itself.

In our case, participation in the CMA Pilot 2 program resulted in a great deal of collaboration across the three major areas, and those are the toxicology, chemistry manufacturing control, and, of course, clinical.

Now, in 2009, due to financial difficulties, Altus Pharmaceutical, who was the original IND sponsor, discontinued their work on the product and transferred it to the Cystic Fibrosis Foundation, and the foundation subsequently licensed the product to Alnara Pharmaceuticals.

In 2010, the NDA was filed and, additionally, in the same year, Eli Lilly and Company purchased Alnara and also acquired the Cystic Fibrosis Foundation's interest in liprotamase.

Liprotamase was developed to address

concerns with pancrelipase or the porcine products, and Dr. Borowitz will discuss these concerns in her presentation.

The initial goal of the liprotamase program was to identify microbial enzymes with similar activity to the overall mammalian pancreatic enzymes. So the candidate enzymes were initially screened in vitro for the ability to nonspecifically digest a broad range of substrates, stability at low pH of the stomach, obviating the need for enteric coating, and to reduce complexity. The optimal enzymes would not require cofactors, including coenzymes.

The final selection of the enzymes was accomplished using a K9 model exocrine pancreatic insufficiency, and the same model was also used to set the ratios of the three enzymes in the final product. So this evaluation resulted in selection of a lipase that cleaves triglycerides at all three fatty acid positions, does not require bile salts for activation, and has no requirement for colipase.

In the case of the protease, unlike the mammalian proteases, the selected protease has no sequence preference and is able to alone produce single amino acids effectively and efficiently from proteins. The amylase is both active and stable across a range of pH values.

Now, shown on the left of the slide, your left, are the structures of the enzymes selected for inclusion. The three enzymes were used in all clinical trials without exception. The lipase is a bacterial enzyme produced using recombinant technology, while the protease and the amylase are both non-recombinant fungal enzymes.

Now, as mentioned previously, a goal of the program was to avoid the use of enteric coatings to enable pH stability. For lipase, this was achieved using new crystallization and cross-linking technology to form lipase-CLEC, and CLEC is an acronym for cross-linked enzyme crystals.

Now, while the protease is inherently stable and active at low pH, it is crystallized in the formulation to prevent it from digesting itself and

the other enzymes in the capsule over product shelf life. On the other hand, the amylase requires neither crystallization nor cross-linking and is present as an amorphous power.

The three enzymes are produced in entirely separate manufacturing trains using conventional biotechnology processes. The three enzyme drug substances are blended together based on activity, along with standard pharmaceutical excipients and dispenses into small size 2 capsules. Each capsule contains the enzymatic activity, as shown here on the slide.

Now, the agency stated within their briefing document that the Phase 2 and the Phase 3 products were not comparable. We respectfully disagree with this assessment. Since we received this comment after our briefing document had already been submitted, I wanted to address the subject at this time before the committee.

So as is the norm for biotechnology products and pharmaceuticals in general, the liprotamase manufacturing process has evolved to better meet

both regulatory and commercial requirements, and these requirements include process robustness, greater product and process reproducibility, which provides increased assurance of product quality, and, of course, appropriate yields.

Extreme care was taken during process development to assure that the actual enzymes manufactured were comparable at each stage of development. Now, since the enzymes are not absorbed, traditional PK studies to confirm this were not useful. Instead, comparability was established using biochemical testing.

Now, in all studies, capsules were filled and subjects were dosed based on enzymatic activity of the three enzymes. The mid-dose used in the Phase 2 study was identical to the dose used in the Phase 3 study. Additionally, compatible with a published FDA guidance, the comparability of the Phase 2 and Phase 3 clinical efficacy and safety data provide further evidence of product comparability, and Drs. Brettman and Stevens will discuss these efficacy and safety data in their

presentations.

So we have submitted a detailed response to the review division and we look forward to resolving this disagreement in the coming weeks.

So, in summary, liprotamase is a novel new molecular entity pancreatic enzyme replacement therapy, or PERT. The product is comprised of three highly active, stable, purified enzymes with broad substrate specificity; a crystallized cross-linked bacterial lipase, a crystallized fungal protease, and an amorphous fungal amylase.

The enzymes are blended with standard pharmaceutical excipients in a stable and convenient capsule drug product formulation. And, importantly, the same three enzymes in drug product formulation were used throughout clinical development.

So with that, I will turn the podium over to Dr. Freedman.

Alnara Presentation – Steven Freedman

DR. FREEDMAN: Thank you, Dr. Burstyn. Just by way of introduction, my name is Steve Freedman.

I've been the director of our pancreas center at Beth Israel Deaconess Medical Center since its inception approximately 22 years ago. I'm also professor of medicine at Harvard Medical School and chief of Division of Translational Research.

My major interests, both clinical, as well as in translational research, have been in chronic pancreatitis, steatorrhea, and with a particularly heavy emphasis on fatty acid metabolism. I also was the lead PI on the 810 study, which examined the role of liprotamase in subjects with chronic pancreatitis and those who have had pancreatic surgery. Otherwise, I have no other disclosures to make related to this compound.

What I'd like to do today is -- and my presentation is twofold, and first is to review with you how exocrine pancreatic secretion, as well as enzyme function, is regulated; and second is how does this evolve over birth, because these two elements are really key in trying to understand a rational approach to pancreatic enzyme replacement therapy.

On this slide, I've put up first some elements about normal pancreatic function. We know, as we've heard already, that this is critical in digestion and, in fact, there's a 90 percent reserve in the pancreas since this plays such a major role.

The enzymes secreted from the exocrine pancreas are active in the proximal small bowel. So, ideally, any replacement therapy should show similar characteristics. Optimum function is dependent on a number of factors, on bile, on pH, on colipase, which is the rate-dependent step, as well as other factors.

What's important is that these factors are altered both in cystic fibrosis, chronic pancreatitis, but also in patients who have undergone surgical procedures on their pancreas. And it's for this reason that many of us who are GI or pancreatic clinicians have had problems where porcine pancreatic enzymes have not been effective as much as we would like.

Here are the diseases commonly associated

with exocrine pancreatic insufficiency, or that we will refer to as EPI, cystic fibrosis, chronic pancreatitis. More and more patients are undergoing -- both children, as well as adults -- partial, but especially total pancreatectomies for either refractory pain of chronic pancreatitis or pre-cancerous conditions, such as IPMN.

We know that malignancy itself, if it obstructs the pancreatic duct, can lead to pancreatic atrophy and exocrine pancreatic insufficiency. And we're starting to see other conditions, such as Shwachman-Diamond syndrome.

I wanted to put up here the two categories that comprise both the symptoms and signs of pancreatic insufficiency. And as we heard from Dr. Mulberg, there are nutritional deficits, which are a hallmark feature of pancreatic insufficiency. These include weight loss and delayed growth that can have a major impact on a patient's clinical course, and this includes both micro, as well as macro nutrient deficiencies.

In addition, we have gastrointestinal

symptoms, abdominal pain, steatorrhea, bloating and flatulence. And what's important is that these are the same symptoms and signs, irregardless of the cause, of exocrine pancreatic insufficiency.

I wanted to also focus on maturation of the pancreas because we know that lack of lipase is the major contributor to these nutritional deficiencies and symptoms in patients with EPI. There are a few papers that have been published that help inform us about this where lipase activity has been looked at. It was found that by at least 2 years of age, lipase activity is the same as that in an adult.

The first paper I'll cite is that by Lebenthal and Lee. This was done around 1980. Probably we couldn't do these studies nowadays in today's environment. But what they did was to take infants starting at term, a week of age, or up to 2 years of age, have an oral duodenal tube in place, give them secretagogues that turn on the exocrine pancreas, and look at what's secreted into the duodenum by collecting the fluid and look at the different enzyme activities. And what was

found was that by age 2, lipase secretion was 210 units per milligram in otherwise healthy infants.

Another paper by Borovicka, et al, looked at healthy adults in their 20s up to age 30, and what you see is that basically the same lipase activity is seen. So this tells us, by age 2, lipase secretion is maximal.

So if we're going to think about rationally dosing in patients, then this tells us that whether you're age 2 or you're age 20, that you're probably going to need similar lipase requirements.

Factors altering the effectiveness of porcine pancreatic enzyme replacement therapies are twofold. One is in fat digestion. We've already heard that a number of factors affect porcine enzymes, low pH, precipitation of bile salts, late release due to enteric coatings. These are all factors, especially in cystic fibrosis, but also in chronic pancreatitis we can see this. In addition, fat absorption can have an impact. This includes gut mucosal factors, bacterial overgrowth, poor

micelle formation.

We're going to hear about this morning much about the CFA as a measurement. What's important to remember is that CFA reflects both of these different elements here, both fat digestion and fat absorption. Fat digestion simply reflects lipolysis of lipase on substrates on food. But confounding our CFA results is the fact that there are other factors that play a role in fat absorption. So if you have an impaired intestinal mucosa, you're going to get increased fast in the stool manifest as a greater abnormality in CFA.

The requirements for optimal enzyme, pancreatic enzyme replacement therapy, ideally, we'd like them active at a wide pH range. We'd like them unaffected by the presence or absence of bile salts, and we ideally would like a lipase that does not require other cofactors, especially colipase.

So to summarize, the problem that we're addressing today is that in pancreatic exocrine insufficiency, it's simply a lack of pancreatic

enzymes, and our goal of treatment strategies is to effectively replace those enzymes. The treatment is the same regardless of underlying cause or of age, at least age 2 and over and higher, and that the dosing in clinical practice by many of us is dependent on two issues; one, the lipase activity of the pancreatic enzyme formulation we're using in our pancreatic insufficient patients, but it's also dependent on the quantity and type of foods and fats that are ingested more so than weight or age.

At this point, I'd like to turn this over to Dr. Borowitz.

Alnara Presentation - Drucy Borowitz

DR. BOROWITZ: Thank you. I'm Dr. Drucy Borowitz. I served as the principal investigator for the studies of liprotamase in Phase 1, Phase 2, and Phase 3 for patients with cystic fibrosis.

My employer, the State University of New York at Buffalo, received reimbursement from the sponsor for my activities related to that, but I have no financial interests and the outcomes of this meeting will not affect me in any way.

I've been a CF clinician and a CF center director for more than 20 years, caring for patients with CF. In addition, I have served as an expert for the CF Foundation for gastrointestinal and nutritional issues, including co-chairing the meeting in 1995 along with the FDA to set guidelines for dosing of pancreatic enzymes; the meeting that Dr. Mulberg mentioned on gastrointestinal outcomes and confounders; and, I participated in the 2008 evidence-based review sponsored by the CF Foundation, looking for evidence for dosing of pancreatic enzymes.

As Dr. Mulberg did, I'd like to point out that CF is a multisystem disease of infections, and the development of obstructive pulmonary disease is a primary factor in the life-limiting nature of cystic fibrosis. But there are other factors that affect quality of life, as well. Ninety percent of patients have pancreatic insufficiency.

There are also gastrointestinal and hepatic complications of cystic fibrosis. Twenty percent of patients are born with a neonatal bowel

obstruction, meconium ileus, and there's another form of bowel obstruction that occurs later in life, distal intestinal obstruction syndrome. And the incidence of DIOS is difficult to determine, because sometimes it's quite low grade and is not reported, but results in symptoms.

Hepatic complications of CF include the rare but very significantly severe sclerosis and portal hypertension and the very common elevation of transaminases, which is intermittent, occurs in a large number of patients, and has no correlation with the development of serious sclerosis and portal hypertension.

Dr. Freedman outlined the symptoms and signs of exocrine pancreatic insufficiency and noted that they are no different in patients with EPI from any cause, but I'd like to talk about it in the context of CF. You can see a picture taken from the first paper published in the English language literature describing cystic fibrosis. The author, Dorothy Anderson, was a pathologist, and she diagnosed CF at autopsy in patients who died of what was thought

to be either celiac disease or vitamin A deficiency. Then when there were subsequent children in those families with similar symptoms, they diagnosed them as having cystic fibrosis.

You can see in these two patients described in her paper the signs of protein calorie malnutrition. The baby on the left has a bloated belly and waisted buttocks. The baby on the right shows you the peripheral edema, with swollen labia. And I put these pictures up to remind you that treatment of exocrine pancreatic insufficiency is life-sustaining. So our treatment for this is with pancreatic enzyme replacement therapy, and, for patients with CF, a high calorie, high fat diet.

A brief history of pancreatic enzyme replacement therapy. As Dr. Mulberg pointed out, porcine extracts were used, starting shortly after the description of this disease for patients with CF; initially, pancreatine, then the more concentrated form of pancrelipase. It was noted that these enzymes became inactivated in gastric acid and required enteric coating.

In the early 1990s, there was dose creep, some of it as a result of the seminal paper by Corey, et al, mentioned by Dr. Mulberg, correlating a high calorie, high fat diet with survival. So there was a sense that there was no upper limit to using enzymes and that more was better, and, unfortunately, that was clearly associated with the complication known as fibrosing colonopathy, bowel obstruction that had a clear dose-response relationship.

We don't actually know what the cause was of fibrosing colonopathy. In 1995, the FDA and the CF Foundation held a joint meeting to look after the safety of patients and set weight-based dosing. But what I want you to understand is that although that is expressed in lipase units per kilo per meal or per day, this was a way to look at exposure.

So looking back, the only way we could know what the exposure was, was to base it on weight, which we had evidence for. We were unable to go back and find dietary intake recommendations.

So these were weight-based dosing to look at

exposure. We don't actually know what the exposure was that caused DIOS. Was it lipase, protease, unlabeled enzymes, excipients, coatings? That's not clear.

In 2008, the CF Foundation commissioned an evidence-based review of the world's literature looking for data upon which to base dosing recommendations, and in this intervening period of time, insufficient evidence was found to make any new recommendations about dosing.

I'd like to talk a little bit about CFA, the endpoint that we're going to discuss today. This is a short-term measure. It's the surrogate endpoint that's accepted by the FDA. However, no correlation has been found between any specific CFA cut-point and a clinically meaningful endpoint. Multiple factors affect digestion and absorption, as Dr. Freedman mentioned, and can also affect CFA.

This is a scatter plot taken from patients who were studied clinically at the Hospital for Sick Children in Toronto, perhaps the only place in the world where people use CFA on the clinical

basis. This is not a study that's done on any regular basis in care of patients with CF.

What you see along the Y-axis is dosing of pancreatic enzymes expressed in units of lipase per gram of fat; and along the X-axis, coefficient of fat absorption. I've drawn a dotted line at 80 percent, and I want you to see two things on this slide. One is that there's a scatter here. There's no correlation between the dose of pancreatic enzymes and CFA. And second is that many patients have a CFA on pancreatic enzymes which is less than 80 percent.

Some of the studies that you've reviewed looking at porcine products specifically exclude patients whose CFA on enzymes is less than 80 percent, and we are going to show you data as this day goes on in an unrestricted patient population.

I do want to point out you're going to hear us talking about our exclusion of patients who had a CFA off of enzymes of greater than 80 percent, and so this off-and-on thing is important to keep

in your head. So off enzymes, CFA is used as a diagnostic test for exocrine pancreatic insufficiency, and if your CFA off of enzymes is less than 80 percent, you have severe EPI in the setting of CF.

Dr. Mulberg also showed this slide. I think it shows how important the issue of growth is, especially in children with CF. We've seen improvements in growth as a result of some of our quality improvement and other measures in the CF population. But despite this, there is an inexorable decline in growth over the ages between about age 4 to age 14, and this is a worrisome factor. As Dr. Mulberg pointed out, there is a tight relationship between growth and survival.

This is cross-sectional data, but I want you to keep it in mind, because during this period of time, patients do lose weight and they lose ground.

This data also comes from the CF Foundation's patient registry, which, I should point out, is data-generated from the 120 accredited CF centers around this country. Patient

data is put into the registry. There are over 20,000 patients in the registry. And this shows the very tight association between growth as expressed by body mass index and lung function as expressed as FEV1, forced expiratory volume in one second, a measure of airway obstruction. I've shown you the data for patients aged 2 to 20, but the curve looks very similar for adults, as well.

We're going to talk about growth over the course of the day, and in our study, we looked at a patient population that ran from very young children to adults. And so we have used Z scores as a way to express the growth over that large population.

On the left is a BMI percentile chart for patients aged 2 to 20. And what I want you to see is that the rate of growth is different at different times of age. So in young children, in children in the teenage years and in adults, that rate of growth is very different. The skew around the mean is also different, and so Z scores are used as a way to normalize that data, regardless of

the rate of growth or the age.

When looking at BMI Z scores, weight Z scores, height Z scores, a flat line means that things are normal, that the rate of growth for your particular age is normal. So straight is good.

In the development of a new molecular entity such as liprotamase, you need complementary things. So CFA is a good measure for short-term studies, especially to do dose ranging to identify a minimally effective dose and to demonstrate short-term efficacy. But a long-term clinically meaningful measure is also useful when talking about a product that's going to be used over a lifetime. And so growth as expressed by either body mass index, weight or height is also used, and we'll show you data.

Why is it important to develop a new pancreatic enzyme replacement therapy formulation? Let me just outline a few of the issues. There are sourcing and supply concerns. Porcine products are dependent on pig herds. If, for some reason, pig herds need to be culled, that would put at risk

this life-sustaining therapy for patients.

You may have read the news yesterday. The German government required pigs to be slaughtered because of dioxin in feeds in a variety of pigs that was found to be at levels in pig products that were harmful to humans, and I think we'll hear more about that as this week goes on.

There also were concerns about transmission of pathogens from porcine sources, and there are issues with consistency of manufacturing. Now, some of those have been dealt with, with the new drug applications, but there are certain things that are inherent to using an animal-derived product.

For example, the ratios of enzymes are fixed. They are what they are in pigs. And there are three to four times as much protease relative to lipase in porcine enzymes. That's not the way it is in humans. Things that come from tissues such as pancreas that are rich in DNA have purines in them, and that's just an inherent part of these extracts.

Pill burden is another real issue. We're happy that patients with cystic fibrosis have been living longer and more productive lives. And so adherence to this complex regimen is an issue. In one study looking at adherence to recommendations, fewer than 50 percent of patients were taking their pancreatic enzyme replacement therapy as prescribed. This is likely a major factor in ongoing symptoms and malnutrition.

In data from the CF Services Pharmacy in over 3,000 patients, a mean daily dose of enzyme capsules was 16.7 to 25.7 per day, depending on age. In addition, as was pointed out, porcine enzymes do not have stability in an acid environment and need to be enterically coated, and so that has some issues in terms of delivery of drug.

So the development goals for liprotamase were to demonstrate safety and efficacy with a reliable source with reproducible and a precise manufacturing process, with a product that has no excess protease and no purines, a lower daily pill

burden with a product that's acid stable and does not need enteric coating, and for which we will have a data-driven approach to dosing.

So with that, I'm going to turn this over to Dr. Brettman, who will tell you about the results of the liprotamase studies.

Alnara Presentation - Lee Brettman

DR. BRETTMAN: Thank you, Drucy. My name is Lee Brettman. I'm the chief medical officer of Alnara Pharmaceuticals. I'd like to start with a brief overview of what I'm going to discuss with you during this portion of the presentation.

I'm going to take you through the short-term efficacy studies where CFA was the primary efficacy endpoint; the long-term clinical activity studies showing a BMI, height and weight over time; and, then I'm going to come to one of the questions that the FDA has asked the panel in dosing guidelines. I'm going to address both dosing in 7 and older, but also the rationale for extrapolation of dosing to children 2 years to less than 7 years of age, as well. And, finally, I will address the issue of

the CFA.

The FDA has raised the issue that since the CFA we observed in our study was not 30 percent change from baseline, that there is reason to believe that this is not an adequate CFA. We disagree with that, and I will address that at the end of my presentation.

So liprotamase overview. In the short-term studies, TC-2A and 726, we identified an efficacious starting dose in two adequate and well-controlled studies that consistently met their primary and secondary study objectives. We met clinically meaningful long-term goals of replacement therapy. The reason replacement therapy is given is to maintain nutrition.

Nutritional status was maintained in 767 and 810, and in the 767 study, we will show you data that shows that liprotamase supports age-appropriate growth and weight gain in children. And very importantly, as the FDA has pointed out in their document, maintenance of pulmonary function is very important, as well, and we will show you

data that pulmonary function was maintained as measured by FEV1.

Finally, as Dr. Borowitz pointed out, it's very important to have data that guides dosing. And so the liprotamase program delivers that information, establishing that initiating treatment with one capsule per meal or snack is an appropriate starting dose for chronic therapy, with individualization of dose if necessary, as is done with other replacement therapies.

In my presentation today, I'm going to focus on four studies. Overall in the liprotamase program, seven studies were done, including dose ranging studies, and enrolled overall 492 unique subjects. Some subjects were enrolled in more than one study.

I'm going to focus on the short-term efficacy studies, TC-2A, which enrolled 125 subjects; 726, which was an international study that enrolled 163 subjects; and, then, the supportive long-term study, 767, again, an international study with many severely

nutritionally compromised subjects, as well as the 810 study, which presents the data for subjects that have EPI due to other causes, such as chronic pancreatitis and following a pancreatectomy.

TC-2A and 726 share common entrance criteria. They were both studies of EPI in patients with cystic fibrosis. They both enrolled patients or subjects 7 years of age or older. The diagnosis of EPI was made based upon a fecal elastase of 100 micrograms per gram of stool or less.

There was a weight restriction in TC-2A because of the fact that a very high dose of liprotamase was included in that study and would have exceeded the CF guidelines. There was no such restriction necessary in 726 for the reason that a lower dose was selected as the appropriate starting dose.

Baseline CFA Dr. Borowitz mentioned. There was a restriction in 726. There was an off-enzyme measurement of CFA. So without the benefit of enzymes, CFA was measured in all patients before

they went into either the TC-2A or 726 study. And in 726, if subjects had an off-enzyme CFA greater than 80 percent, they were not eligible to be randomized due to the fact they were considered not to have severe EPI.

Some other important features of these two studies are that they were both large, parallel group, controlled, randomized trials, the largest studies ever done. Nutritionally and functionally compromised patients were purposefully included because it was very important to Dr. Borowitz, as the principal investigator, and the Cystic Fibrosis Foundation that the data generated in these studies could be applicable to the general population the clinicians deal with in their practices. This is not the patient population included in the porcine products, and I'll come back to this later.

CFA was the primary endpoint measurement. To do this measurement, patients must be on a 100 gram of fat per day diet. And these studies were fixed dose, no optimization was allowed, no adjustment of dose was allowed.

The primary endpoint measurement, as I mentioned, was a coefficient of fat absorption. A 72-hour period of 100 gram of fat per day diet was marked with a blue marker at the beginning and the end of the 72 hours, and then the stool was collected, marked with a marker, to make sure there was complete collection of the stool representing the 72-hour 100 gram fat diet intake.

CFA is calculated in a very straightforward fashion. The fat in the stool is measured over the 72-hour period. That is subtracted from the total fat ingested; over the total fat ingested times 100 yields the CFA percent.

Secondary endpoints included coefficient of nitrogen absorption done in the same fashion as CFA and supportive secondary endpoints, including stool weight, stool frequency. And there was also a starch challenge exploratory approach incorporated in the studies, but I will not talk about that further because it was exploratory. The doses for TC-2A were selected based on the dose ranging study, TC-1B. In the simple table at the

top here, you can see that five different doses were studied, ranging from 100 units of lipase -- and by the way, I should mention, when I talk about liprotamase, I'll be referring to it in terms of the lipase strength, although it contains protease and amylase. So there were five different doses of liprotamase studied ranging from 100 units per kilogram per meal up to 5,000 units per kilogram per meal; so a 50-fold range in the dose ranging studies.

You can see that there's a breakpoint between the 100-unit dose and the 500-unit dose, after which there was a relative plateau. This is supported by the secondary endpoints measured in this study, as well. And on the basis of this, the following doses were selected for use in TC-2A; the 100 unit per kilogram per meal dose, which translates to 6,500 units per meal; the 500 unit dose, which translates to 32,500 units of lipase per meal; and a dose fourfold higher.

The schematic of this study is shown here. Subjects, all of whom were on porcine enzymes, were

taken off of those enzymes at the beginning of a three-day off-enzyme period and put on the 100-gram of fat per day diet, and a marker-to-marker stool collection was done to assess the primary and the secondary endpoints.

Then subjects were randomized to receive one of the three doses of liprotamase, and after 14 days on that dose, they were brought back into a clinical research center for another marker-to-marker stool collection in the same fashion.

Subject disposition and baseline demographics are shown on this slide; 129 subjects were randomized, 125 were treated and comprised the intent-to-treat population. The mean age of this group was 21.3. And I just want to draw your attention to the BMI Z score, which is about half a standard deviation below the norm for the normal U.S. population. So this is a nutritionally compromised group of patients.

Here you can see the mean change from baseline CFA in the intent-to-treat population. The design of this study was a comparison of doses,

and you can see that the mid-dose of 32,500 and the fourfold higher dose were both significantly superior to the low dose.

This is the CNA results. It shows exactly the same picture. So consistent results of liprotamase by CFA, BY CNA, and, in addition, we see the same picture with the reduction in stool weight. This is an important parameter because it correlates with steatorrhea.

So, in conclusion, TC-2A, liprotamase met its primary endpoint of significant improvement of fat absorption. It met key secondary endpoints, protein absorption, decrease in stool weight. And liprotamase 32,500 was selected as an appropriate efficacious starting dose for confirmation in the 726 trial and for initiation in the product trials, which started contemporaneously.

726 was the subject of a special protocol assessment with the FDA. It was to be a randomized, double-blind, parallel group study, a comparison of liprotamase 32,500 units versus placebo. The primary analysis population was to be

subjects with a baseline off-enzyme CFA of less than 40 percent because these were considered to be the most severely affected.

The least squared mean difference, or LSM, in CFA compared to placebo was the primary analysis. The secondary endpoints were considered supportive and, as I mentioned, subjects with CFA greater than 80 percent during the off-enzyme period were excluded.

The schematic for 726 is shown on this slide. In this study, there was a six-day off-enzyme period where subjects were brought into a clinical research center and, again, the marker-to-marker stool collection with 100 gram of fat per day diet. They were then on an open label period of liprotamase from 21 to 31 days, and they were brought back in for a repeat of the marker-to-marker during the third, fourth and fifth days of that six-day inpatient period.

The disposition for this study is shown on this slide; 163 subjects were treated, 138 were randomized. The major reason why subjects were not

randomized was due to a baseline CFA greater than 80 percent.

Now, I want to highlight the demographics of this study because I think it's very important, and that is that many nutritionally compromised subjects were included in these studies, subjects that are typically excluded from the study cited in the FDA Table 4 of their document and in other studies of porcine PERTs.

What you can see here is this was an international study, 68 subjects in the United States, 45 in Eastern Europe, 25 in other non-U.S. countries. And I would particularly direct your attention to the Eastern European column. The mean age of these subjects was 13.5, and yet their BMI Z score was minus 0.869, or the 19th percentile, very severely nutritionally compromised subjects.

When you look at a definition of nutritional compromise that has been used to exclude subjects from some porcine PERT studies, you can see the percentages that were included in this study, and that definition is a BMI of less than 20 milligrams

per meter square for subjects over 18 years of age or below the 25th percentile for those below 18 years of age. Overall, close to 40 percent of the subjects in this trial met that nutritional compromise definition.

Here are the primary efficacy results from the primary analysis population of subjects with a baseline off-enzyme CFA of less than 40 percent. And let me just orient you as to what's on this slide.

So above the bars is the least squared mean difference between liprotamase and placebo. That was 15.1, highly statistically significant; in addition, in the green bar and in the gray bar, the intra-treatment differences. So this is a comparison of the patients' off-enzyme value to their randomized either on-treatment or placebo value. So it's more comparable to a crossover value.

In addition, when you look at the overall population for those subjects that had a CFA greater than or equal to 40 percent at baseline,

you see the same story, very clear, unequivocal statistical superiority of liprotamase over placebo.

The same story is told by CNA. I won't take you through the results on this study. I think they're self-explanatory. Stool weight, once again, tells the same story. Liprotamase is significantly superior to placebo.

Now, there were prospectively defined subgroup analyses in the 726 protocol. There were eight different subgroups analyzed, geographic region, U.S. versus non, age 7 to 20, greater than 20, and you can see the others here, on-off acid suppression. And the point I would like to make is that in all of these eight subgroup analyses, the point estimate favors liprotamase, and in seven of the eight, it is significantly superior.

When you look at the intra-treatment difference -- again, this is the comparison of an individual's off-enzyme value to their on-liprotamase value -- you see a very similar story. All of the point estimates favor liprotamase, and

in this case they are all statistically significant.

Now, Dr. Burstyn mentioned that we believe the material used in Phase 1/2 is comparable to Phase 3, because the capsule strength was based on activity, and the dosing used in TC-2A is identical to that in 726, based on lipase activity, protease activity, and amylase activity.

So across these two studies, in the primary analysis population from 726 of less than 40 percent baseline CFA, there was a highly significant superiority of liprotamase over placebo. And, once again, in the green bar, you can see in the TC-2A study, which was done in the United States only, that difference was 36 percent, and in the 726 study overall, it was 21.2 percent.

When you look at just subjects in the U.S., which is, obviously, of special interest here today, the story is the same. TC-2A is unchanged, because it's a U.S.-only study, and you can see that the intra-treatment difference in the 726 study in the U.S.-only subjects was 22.7; so clear,

unequivocal statistical superiority of liprotamase over placebo.

So to summarize the two short-term studies, liprotamase consistently met its primary and key secondary endpoints. The 32,500 unit dose was consistently superior to control and in the subgroup analyses that I showed you; and, that liprotamase is an appropriate and efficacious starting dose for chronic therapy.

Now, the FDA, in their briefing document, has very importantly pointed out that if a CFA were inadequate, one might expect to see issues with growth or with pulmonary function. And the 767 study allows us to address those concerns and show you that liprotamase maintains nutrition and pulmonary function over periods of up to 12 months in a very severely nutritionally compromised population.

Let me turn to those studies. The two studies are shown here. Study 767, which enrolled 214 subjects, it's the only long-term prospective nutritional study ever done of a replacement

enzyme. As you can appreciate, that's a double-edged sword, but we think the data is very strong and I will take you through it. This enrolled subjects with EPI due to CF. 810 enrolled 39 subjects with EPI due to chronic pancreatitis or pancreatectomy, with an age range of 27 to 82. So, overall, 253 subjects in these two studies, with a very broad range of ages.

A simple overview of Study 767 is shown on this slide. The primary objective of this study was to evaluate the long-term safety and tolerability of liprotamase treatment. The target enrollment was up to 200 subjects, with at least 100 completing 1 year of age and with a good representation of children 7 to 11.

Now, I want to point out that there were in the protocol prospectively defined clinical activity measurements, including serial measurement of BMI and weight. These were transformed into Z scores, and this was to enable the -- to determine the effect of liprotamase treatment on the maintenance of nutritional status. These were not

unplanned. They were specified in the protocol.

This is a simple schematic of Study 767. The entry criteria were very similar to 726. One thing I would highlight here, as you can see in that green line, subjects from 726 were allowed to roll over into the long-term trial upon completion of their participation in the 726 trial. Eighty-eight subjects rolled over, and during the first six weeks or so of the 767 trial period, they were still on the fixed dose from 726; 126 subjects had not received liprotamase previously.

They then entered the open label flexible dosing phase. And by flexible dosing, I mean they started with a dose of 32,500 per meal or snack, and then the dose was individualized, if necessary, to two capsules per meal, remaining at one capsule per snack, based on the usual considerations used to adjust dose in these subjects, including the occurrence of EPI, related GI symptoms, steatorrhea, abdominal pain, et cetera, and voluntary weight loss or diet.

Now, since this was the first study of its

kind ever done, a lot of data was collected. And in order to put that data into perspective, a post hoc analysis was done where we used the CF registry to enable us to match a group of patients from that database during the same period of time that the 767 study was being conducted, and this group match included the same entry criteria as 767.

All subjects had to be porcine PERT users. So every subject in this analysis was on porcine PERTs. Subjects were 7 years of age or older, and there had to be height, weight, BMI information available at zero time point and then at one year and with at least one determination in between. And very importantly, the CF registry collects information about whether or not subjects or patients require hospitalization.

This is a simple comparison of the baseline demographics between the 767 population and the CF registry population, and you can see they are similar, with about half taking acid suppression. And I would direct your attention to the BMI Z

score line, showing that overall the subjects in the 767 study were more nutritionally compromised than the subjects in the registry.

Now, you see the same pattern in demographics in this study. This was an international study. And, once again, I want to direct your attention to the U.S., 112 subjects, 56 from Eastern Europe, 46 from other non-U.S. countries. The mean age of the Eastern European subjects, once again, is very young. And in spite of being young, they have arrived at a very nutritionally compromised place on their existing therapies at the time of enrollment into this study.

Again, on the bottom line, using the same definition of nutritional compromise used to exclude patients from some porcine PERT studies, you can see, again, a very high proportion of the subjects in this study were nutritionally compromised by that definition.

Now, this is a comparison of the CF registry to the 767 data for the BMI Z score. We also have

the same information for height and weight Z scores, and it shows the same pattern. But, first, here is the registry population. All of these subjects are on porcine PERTs.

When you look at the U.S. portion of the 767 population, which is here, the lines are essentially superimposable. So the pattern looks the same over time, showing that in this population of patients in the CF registry, the subjects in the 767 trial in the U.S. show a similar pattern over time.

Now, you see some interesting differences, as I've highlighted in the demographics, with the other non-U.S. and the Eastern European patients. So I'll particularly direct you to the yellow and the green lines of the other countries, other non-U.S. countries, and Eastern European, that these are severely nutritionally compromised subjects. These are subjects who were in decline at the time of their enrollment into this study, and you can see consistent results over time. By the way, regardless of acid suppression status, regardless

of whether they completed the study or dropped out early, the pattern was the same.

Now, the FDA has pointed out in their briefing document that there is an initial decline in these Z scores, and that is true, but I want to give you some more insight into what is driving that.

We did an analysis where we looked at subjects who had a 5 percent weight loss by month 3 of the study, early weight loss. There were 23 subjects who had 5 percent weight loss. And you can see the pattern here, and you can see very clearly that that weight loss occurred early but then stabilized. So the weight loss was not progressive. That's very important.

When you remove those subjects from the 767 data, you don't see the initial dip. It's these 23 subjects that are driving it. And let me make a couple of very important points about these 23 subjects. Nineteen of the 23 were non-U.S. subjects, so only four of the subjects in the United States experienced this weight loss.

Thirteen of these 23 completed the study. So I think those are very important points and put into perspective what's actually going on early on in the study.

Now, the other important point is would there be a deleterious impact on pulmonary function as measured by FEV1, and I think the answer to that is clearly no. This is the FEV1 data from 767, showing baseline, six-month and 12-month determinations, and this shows you that it was quite stable over time.

Now, let me move to Study 810. The key entrance criteria for this study were that subjects had to be 18 years of age or older and have EPI due to chronic pancreatitis or pancreatectomy. The diagnosis of EPI was similar to that of the other studies I've mentioned, but they could also enroll in the study if they had a history of steatorrhea, weight loss, diarrhea, and be on replacement enzyme therapies for at least three months before entry; a very simple study schematic. The starting dose was the same as in the 767 study and with the same

guidance as to adjustment of the dose.

Forty-one subjects were enrolled in the study; 39 comprised the intent-to-treat population. Dr. Burstyn mentioned in his presentation that the conduct of the liprotamase development program was discontinued by the previous sponsor. That was due to financial difficulties. They were not financially able to continue the studies, and that is why it was discontinued.

In spite of that, 74 subjects completed three months and 25 had a median time on study of 25 weeks. So this is still a very robust database. Seventy-seven percent of these subjects had chronic pancreatitis and approximately a quarter had EPI due to pancreatectomy.

In adults, looking at weight over time is a more important parameter perhaps to look at than BMI, and, again, you see the same pattern of maintenance of nutrition with liprotamase, particularly through that month 3 period when the vast majority of the -- or the majority of the subjects are still enrolled.

Let me move now to the dosing guidelines, and I will address here the rationale for requesting labeling in children 2 to less than 7 years of age. I want to start with a summary of the dosing in 767 and 810. You will remember that dosing started with one capsule per meal or snack and then could be increased if necessary based on symptoms, diet, et cetera.

Overall, in the 767 study, average capsules per day was 5.5; and, in the 810 study, it was 4.1, reflecting the fact that these older subjects aren't having three meals and two snacks a day necessarily.

The maximum average capsules per day in the 767 study for any subject was 10.6, and, similarly, it was 10.5 in the 810 study. And in the 767 study, this did not exceed or, in fact, come close to the CF guidelines for maximum dose of lipase.

So I won't go over this in detail. I think I've covered this earlier. But the starting dose, with individualization of dose if necessary, and the guidance for upper dose should be not to exceed

the CF guidelines, and additional dosing guidance would be in the label based on the 767 study.

Let me move now to the rationale for extrapolating the liprotamase data to children 2 to less than 7 years of age. First of all, as Dr. Freedman pointed out in his discussion, the physiology of the pancreas and, in fact, the gut is mature by approximately age 2, and so that would be comparable in these younger children, older children, and adults.

The pathophysiology of exocrine pancreatic insufficiency is the same. The problem is a lack of enzyme. The treatment is to replace those enzymes. We have a very large prospective safety and efficacy database in children and adults. And when you look at the 767 data by age, 7 to less than 12, 12 to less than 17, or overall, you can see, regardless of age group, the nutritional pattern is the same with the maintenance of nutrition.

Finally, a couple of other points that are particularly relevant here are that enzymes digest

food in the gut, and they're not systemically absorbed. That's important from a safety perspective.

The regulatory precedent for extrapolation with porcine PERTs is also quite strong based on many of these arguments. I won't go into that here, but would be happy to address any questions about that later. But it leads to a very simple dosing guideline for children 2 to less than 7 years of age. The starting dose should be based upon average fat intake. The capsules may be opened and the contents mixed in 5 mils of water or other fluids, such as apple juice. And then, based on average fat intake for patients 2 to 3 years of age, which is 40 to 50 grams, or 3 to 7, which is 60 to 70 grams, this leads to a very simple dosing paradigm, as you can see here, not to exceed the maximums of the CF Foundation.

So let me move now to I think what's the most controversial issue that we'll talk about today, and that's the CFA. As Dr. Borowitz pointed out, CFA is a valuable short-term surrogate

measure. It can demonstrate the difference between effective treatment and placebo or in an effective control. However, and I think the FDA and the sponsor agree on this, the degree of improvement in CFA that is required for clinical benefit is unknown, because there are no studies correlating the magnitude of change in CFA with long-term clinically meaningful outcomes.

So I want to address the design and patient selection for the porcine studies that the FDA has used for a comparison to liprotamase. Design and patient selection will dictate and predict what the CFA that we've measured in those studies will be, and let me explain what I mean by that.

First of all, in design, these are typically small crossover studies of 30 to 40 subjects, so a very small patient population. In fact, one of the studies in the table that the FDA provided is a responder study, meaning the subjects were put on the drug to be tested. CFA was measured while taking that drug, and if they did not have a CFA greater than 80 percent, they were excluded from

randomization. There is no way that type of study can be compared to the liprotamase studies.

In addition, the doses studied across the board in these studies were very close or at the maximal dose in the CF guidelines for units of lipase per gram of fat.

Subject selection, another very important issue. Stable patients only were typically eligible. Nutritionally compromised patients were often excluded, and symptomatic patients during the -- they all had a dose titration phase where the dose was adjusted to maximize response. Patients who continued to be symptomatic during that period in some studies were excluded, and these studies were done only in the United States. And I think you could see the impact of doing an international study in terms of the nutritional compromise and the diversity with regard to nutritional status in such a study. And so it is inappropriate and misleading to compare results from these studies to liprotamase.

One final point I would make about this is

that the design and subject selection in these studies actually worked pretty well. Ninety to 100 percent of the subjects in these studies achieved a CFA greater than 80 percent. And as Dr. Durie, who is here with us today, can tell you -- and Dr. Borowitz pointed out that his center is one of the only ones that does CFAs on a regular basis -- only a third of his subjects achieve a CFA greater than 80 percent. On this basis, we really feel this comparison is not helpful and actually misleading.

So let me just sum up and take you through the data that shows that across two studies, TC-2A and 726, we saw significant improvement in CFA in the United States. And when you look at 726 alone, let's -- we disagree with the FDA that the Phase 2 material is not comparable to the Phase 3, but let's say you take out the TC-2A data and just look at 726. 726 stands on its own.

The results that you can see here, statistically significant improvement in CFA versus placebo, and you can see the differences in the bar, 15.3, 22.7. In fact, these are the types of

CFA results one should expect in the population of patients that we studied.

Now, let's move on and look at the subjects that rolled over from Study 726. These are subjects who had a CFA measured prior to being enrolled in the 767 study.

The rollover subjects here are shown in yellow, and you can see there's no difference in the BMI Z score pattern compared to the naïve subjects. We have analyzed this data in a number of ways. We've looked at baseline CFA above and below a median, on-treatment CFA above and below a median, change from baseline above and below the median; and, again, all of these groups have similar nutritional status patterns of maintenance of nutrition over time.

Now, I showed you earlier this graph, but I think it's very important. Yes, the CF registry analysis was a post hoc analysis, but it's a very relevant way to think about the data from 767, the first ever long-term nutritional study to be done. This is the registry population. This is the U.S.

population from Study 767; really directly superimposable, regardless of whether subjects were taking acid suppression, regardless of whether they completed or did not complete the study.

Finally, as the FDA has indicated, if the CFA results we demonstrated were not clinically relevant or clinically important, then one might expect a decline in pulmonary function; did not see it. So this is, we believe, very strong data that shows our CFA was clinically meaningful, and we have the long-term nutritional data, the reason these enzymes are given, to back it up.

So let me sum up by saying we've identified an efficacious starting dose, and we confirmed that dose in the TC-2A and 726 studies, where liprotamase consistently met primary and secondary study objectives. We met clinically meaningful long-term goals of replacement therapy, the reason these enzymes are given.

Nutritional status was maintained, age appropriate growth and weight gain in children, and maintenance of pulmonary function. And we have

established dosing based on the data from these four studies, that the appropriate starting dose for 7 and older is 32,000 units per meal or snack, and the dose can be individualized if necessary.

I'll turn it over at this point to Dr. Stevens to take you through the safety presentation.

Alnara Presentation - Christopher Stevens

DR. STEVENS: Thank you, Dr. Brettman. My name is Chris Stevens. I'm an adult gastroenterologist, and I'm Senior Vice President of Clinical Development at Alnara Pharmaceuticals. I'm going to review the summary of safety in the next 20 minutes or so.

This is how I'm going to present the summary of safety. I'm going to demonstrate the safety by exposure, grouping short and long-term exposure by the trials you've heard outlined by Dr. Brettman; going to discuss generally safety; and then finish up with safety topics of special interest, and then touch on the risk management plan going forward.

Here is the safety population of Phase 1 and

short-term studies and long-term studies. The short-term studies range from 28 to 44 days; the long-term studies, up to a year. I'm going to focus on those short and long-term studies of the safety database of 492 unique patients.

Short-term studies, here we have the safety population for TC-2A and 726, with the corresponding study design shown below, showing the dose ranging study ranging from 6,500 to 130,000 units of lipase, a 20-fold increase over this dose ranging study.

In 726, I show the design here again to remind the panel that all subjects in 726 did receive liprotamase. That's 163 subjects. There was no true placebo arm. There was a placebo period of six days where they were randomized to either liprotamase or placebo during this period. And the reason for that short period was because of safety and ethical issues of keeping patients off enzymes for longer or on placebo for longer than six days.

Here are the serious adverse events. Let me

say there were no deaths in the short-term studies. There were two deaths in the long-term studies, which I will detail when I get to the long-term studies. And here you can see by body system any SAE over the dose ranging study. In TC-2A, there was no dose association of any SAE. You can see here, infections and respiratory led the way as far as SAEs in both the short-term studies, reflecting the underlying study population of cystic fibrosis, with having CF pulmonary exacerbations.

Here are discontinuations due to AEs. Again, across the dose ranging study, you don't see any dose association of discontinuations in TC-2A, and you can see the discontinuations for 726. Gastrointestinal events led the way. Most of these were due to abdominal pain and EPI-related GI symptoms.

Now, I'm going to focus on the 726 study and show the adverse events from the placebo period to the liprotamase period. Here are the six days, and you can see here by, first, SAEs, any SAE were very few and really no difference between the two

periods.

Common AEs, again, by the six-day placebo and liprotamase period, gastrointestinal was the most predominant. But as you go down the list, you can see, in all cases, except for one body system, that the rates were lower in the liprotamase group rather than the placebo group.

Discontinuation due to AEs, by the same presentation here, placebo and liprotamase, AEs leading to discontinuation were comparable across the two arms.

Now, I'm going to focus more on the long-term safety profile and exposure. Here is the safety population. You can see, in 767, 214 patients, 145 completers; in 810, chronic pancreatitis and pancreatectomy, which 28 subjects had greater than or equal to three months, fewer subjects thereafter due to termination of the study by the prior sponsor.

Deaths in the long-term studies, there were two deaths, one in 767 and one in 810. The death in 767 was a 25-year-old male who developed a

pneumonia and was hospitalized, and subsequently developed staph sepsis and succumbed. This was after 11 months on study of treatment. And in Study 810, there was a 62-year-old male that, unfortunately, died in a house fire. Both of these deaths were unrelated to study drug.

Going now to serious adverse events in the long-term studies for any SAE. You can see the percentages here, 28.5 for 767 and less so for 810. Again, infections and respiratory SAEs led the way for the 767 study, reflecting the underlying population of cystic fibrosis. Other SAEs were low.

Most of those -- overwhelmingly, almost all of those SAEs were a result of hospitalizations, and here we have an opportunity to bring in the registry data, which was identified by Dr. Brettman. And here you can see in the blue bars are the registry matched population showing for hospitalization for any cause compared to 767 population. This is on an annualized rate. You can see the hospitalizations for any cause, for

pulmonary exacerbation, for hospitalization due to GI complication, are quite comparable across these two comparisons.

Looking at common AEs for the two long-term studies, open label studies, over the year-long period, you see the gastrointestinal complaints, again, were at the top of the list, followed by infections and respiratory. You can see the imbalance again between 810 for those reflecting the underlying CF population. I'm going to focus a little bit more on the gastrointestinal common AEs, as they were the most common, in subsequent slides.

Here you see now the incidence of GI AEs over time. This is going out on the X-axis, all the way out to 52 weeks and, also, graded by severity, by mild, moderate and severe, by the color coding. These gastrointestinal adverse events occurred early and then decreased over time, and you can see there's a low rate of severe adverse events.

Now, focusing more specifically on the EPI-related adverse events that Dr. Freedman mentioned,

symptomatology of exocrine pancreatic insufficiency, of abdominal pain, steatorrhea and diarrhea, and flatulence, here, shown for each of those preferred terms over a four-week period, you can see the trend down for each of those terms within one to two to three and four weeks of therapy, as shown.

Looking at reasons for discontinuations here, also, broken out by age and the total on the far right column, 32 percent of subjects in 767 discontinued. This was under the forecast of expected discontinuation rate of 36 percent when the study was designed, based on other long-term CF studies including children. And you can see the adverse event discontinuation rate was 17 percent overall. If you look at these rates broken out by age, you can see that actually the discontinuations were higher overall and for AEs in the greater than or equal to 17 age group, less so in the children.

Looking at the Kaplan-Meier for the time to discontinuation over the weeks of treatment, you can see that the discontinuations occurred early,

and those patients that stayed in through week 12 to 16 remained in the study.

Now, I'm going to switch gears a little bit to talk about safety topics of special interest to EPI and to cystic fibrosis. The top two I'll just touch on here. Fibrosing colonopathy and hyperuricosemia and hyperuricosuria are actually issues that have been developed with the porcine products.

The fibrosing colonopathy is an inflammatory and fibrosis condition of the colon that can result in stricturing and lead to colectomy and sometimes death. This has been associated with high doses or high strengths of porcine products. Hyperuricosemia and hyperuricosuria has been an issue with the porcine products due to the fact that you get a high purine load from the pancreatic extract, and sometimes this can result in gout flares. We did not see any fibrosing colonopathy in our program nor did we see any hyperuricosemia or hyperuricosuria.

Distal intestinal obstruction syndrome and

transaminase elevations I'll focus on a little bit more. Distal intestinal obstruction syndrome is a problem with CF subjects who have pancreatic insufficiency from clogging or partial small bowel obstruction, or even complete small bowel obstruction, with muco-feculent material, usually related to off-enzymes or under-dosing of enzyme replacement therapy.

So I'll talk a little bit more about distal intestinal obstruction syndrome in our program. We did see this. We saw seven episodes of DIOS in six subjects -- one subject had two episodes -- here in the 433 CF subjects. Three of the subjects did continue on treatment with no recurrence and there were no surgeries or deaths due to DIOS in the program.

If you look at the annualized incidence of DIOS, in all of our studies, it was 3.4 percent, and in the long-term study, it was 1.9 percent. So to put this into context of the literature, it ranged from 3.8 percent annualized up to 22 percent. So we're below the range of DIOS in

comparison to the literature.

Looking specifically at these subjects here, first, in the short-term studies, we had three in TC-2A and one in 726. But if you look at the middle column, the most important thing here is that the symptoms actually began in the off-enzyme period for three out of the four, and the fourth one, the top one, was actually on an ineffective dose of liprotamase in the TC-2A study of 6,500 units. Also, note that these patients, in addition to having these symptoms off-enzyme, received very low doses or very few doses of liprotamase, particularly, one, three and four doses, respectively.

So that's the short-term studies. In the long-term experience, we did see three subjects that experienced DIOS. One subject had a history of meconium ileus and also had DIOS in TC-2A. Patients that have DIOS tend to be repeat offenders and continue to have DIOS subsequently.

The other two subjects had DIOS that was managed as an outpatient. They were not

hospitalized, and they were treated effectively with cathartics, and they continued in the long-term study without recurrence.

So for DIOS, we did see it. Our annualized rate was lower than what was expected, and in the short-term studies, it was very much associated with being off enzyme therapy.

Now, switching gears to transaminases. As an overview of liver disease and cystic fibrosis, transaminase elevations are seen. As Dr. Borowitz mentioned, this is liver disease, and actually patients who are getting transplanted is an emerging problem, as patients live longer with cystic fibrosis. So you will see transaminase elevations quite commonly in these patients, and in the literature, it's up to 40 percent.

Transaminase elevations, like a lot of chronic liver diseases, are not predictive of disease severity or predictive of progression of liver disease. And, in fact, quite a few patients, up to 7 percent, will actually go on to get severe liver disease or sclerosis. And, interestingly,

the median age of diagnosis is on the younger side, median age of 10 years.

Ursodeoxycholic acid, I mention it here because this is used as a treatment for suspected CF-related liver disease. It's a little controversial whether it's effective, but many practitioners do add this in as therapy for enzyme elevations in presumed CF-related liver disease.

So how do we determine hepatotoxicity? This is a scattergram or an eDISH plot evaluation of drug-induced serious hepatotoxicity. You can see here on the X-axis, there's a peak ALT measure of a given subject and plotted against a peak of total bilirubin, with the bars there showing two times upper limit of normal for bilirubin, three times upper limit of normal for PKLT. And if you match those criteria, you end up in the upper-outer quadrant, so called Hy's Law case.

Now, we superimpose our data here from the two short-term studies, TC-2A and 726. You'll note that there are no cases that meet the criteria for Hy's Law. We did have patients with elevated

transaminase, as you can see out there, and we want to look at those outliers in some more detail. Here, in the Study TC-2A, firstly, we had six subjects that had ALT or AST greater than five times the upper limit of normal. And if you break these subjects down, two were in the mid-dose, or 32,500, and both of these patients already had preexisting elevations at baseline greater than two times the upper limit of normal.

Four subjects were in the high dose, and if you look at those subjects, two of those had elevations at baseline. One was greater than five times and, also, both of those were on ursodeoxycholic acid, suggesting that a practitioner put them on that medication for possible CF-related liver disease.

None of these subjects with these elevated transaminases had an association with a bilirubin increase, and all of these patients stayed in the study and they did not withdraw for these elevations.

Shifting to 726, transaminase elevations,

there were four subjects greater than five times the upper limit of normal. Two had elevations greater than two times at baseline, and one of them was on ursodeoxycholic acid. And, again, same story; none had associated elevations in bilirubin, and they did not withdraw from the study.

Of note, in these short-term studies, there were no restrictions on entry in TC-2A for enzyme elevations; and in 726, the patients could come in as long as their transaminases were below five times the upper limit of normal and total bilirubin was below 1.5 times the upper limit of normal.

Now, looking at the same eDISH plot for the long-term studies, here you see 767 and 810 plotted here, and, again, you see no cases of Hy's Law in the upper-outer quadrant. Again, looking at some of these outliers and elevated transaminases in detail, here, in 767, first of all, 22 percent had elevated transaminases, either ALT or AST, at baseline. Interestingly, 21 percent of patients in this study were on ursodeoxycholic acid.

If you look at the subjects with greater

than five times the upper limit of normal, there were six. One of them was the same subject in 726 that continued on and completed 767. Additionally, a total of four of the six patients with this degree of elevations continued through the year-long study and completed, and four of six actually resolved while on liprotamase therapy.

Of the 214 subjects entered in 767, three of them withdrew for the reason of elevated transaminases. And when you look at those patients' transaminases, they were less than five times the upper limit of normal.

Looking at a summary of transaminase elevations in 810, we had five subjects or 12.8 percent of the population that had elevations at baseline. Two were greater than five times the upper limit of normal, and that elevation occurred after the study drug was stopped, and one subject withdrew for elevations, which was less than five times.

Both of these subjects were chronic pancreatitis patients, and those patients also have

reasons to have underlying liver disease either due to the etiology or their chronic pancreatitis or to obstruction of the common bile duct.

Another way to look at the LFTs and transaminase elevations is to look at the shifts in ALT from baseline to subsequent measure. And here, I put this in the contest of the literature. So here at the top part of this slide is 767, 52-week study, 210 subjects analyzed here that had baseline and subsequent measures; 70 percent had no shift in their measures; 19 percent shifted to a worse grade; and, 11 percent shifted a better grade. Most of those that shifted to a worse grade were Grade 0 to 1.

So how do we put this open label study into context with regard to transaminase elevation? A comparable study, which was 24 weeks, half the duration, was the inhaled tobramycin study. And in that study, we looked specifically at the placebo arm that were not receiving inhaled tobramycin.

In this analysis, performed by Goss and published in the Journal of Cystic Fibrosis,

15 percent had a shift to a worse grade, 12 percent 0 to 1, 3 percent 0 to 2; so very comparable shifts in transaminase elevations, suggesting that these elevations are due to underlying cystic fibrosis-related liver disease.

So to summarize and conclude, for this indication, this is a large, prospective safety database of 492 subjects. We did not see any major organ safety signal or any dose relationship with any safety signals. We did see DIOS. It was of low incidence, lower than what's reported in the literature, and in almost every case, associated with an off-enzyme or an inadequately dosed period. And there's no evidence of drug-related hepatotoxicity. Additionally, because these are microbially sourced enzymes, there's no risk of hyperuricosemia or hyperuricosuria.

Going forward in a risk evaluation, in addition to the regular pharmacovigilance, we are concerned about going forward and, obviously, plan follow-up observational study for DIOS and for fibrosing colonopathy, and we're fortunate enough

to be able to avail ourselves of the already established CFF patient registry.

Risk mitigation, prescribing information will be very important for physicians given the difference in this product and difference in strength and number of capsules used, and there will be an appropriate med guide for patients and caregivers. Other elements of the risk management plan going forward are under review with the agency.

With that, I will turn it back over to Dr. Borowitz.

Alnara Presentation - Drucy Borowitz

DR. BOROWITZ: So at the beginning of this presentation, I outlined these goals for the development of liprotamase. I believe we've demonstrated the safety and efficacy of this product, which has a reliable source with reproducible and precise manufacturing process, no excess protease and no purines, a lower daily pill burden, a product that's acid stable and does not need enteric coating, and we have shown you that we

have developed a data-driven approach to dosing.

The benefits of liprotamase are that we met clinically meaningful long-term goals of pancreatic enzyme replacement therapy. Nutritional status was maintained over one year. There was age appropriate growth and weight gain, a reduction in EPI-related GI symptoms, and maintenance of pulmonary function.

I want to emphasize, these are not just abstract issues. These are things that are highly relevant to individuals with cystic fibrosis.

In addition, we were able to do this with fewer capsules per day. We saw statistically significant improvement in CFA, CNA, and a reduction in stool weight in two large, well controlled trials. And this product was well tolerated, and it had a favorable safety profile.

As with any drug, there are also risks. There's no drug that is risk-free. And if this drug is on the market as an option for patients, there would be similar risks as with the existing pancreatic enzyme products. Not all patients will

respond adequately to products, and therapy needs to be changed at times.

For patients with cystic fibrosis, you can think about this in the context of CF center care. The majority of patients with CF are cared for at CF centers. The national standard of care is follow-up every three months, sooner if there are clinical issues. And at those visits, weights and symptoms can be monitored and, again, the dose could be individualized if necessary.

The number of capsules for this product is less than with the current pancreatic enzyme replacement therapies, and, therefore, it's extremely important to educate individuals with cystic fibrosis and their care providers that this is a very different type of product. And so education, including a med guide, would be important to minimize that risk.

So, in summary, I think that based on the balance of the safety and the efficacy demonstrated from the liprotamase development program, I believe this advisory committee should recommend approval

of liprotamase as an option for treatment of exocrine pancreatic insufficiency.

Thank you.

Clarifying Questions from the Committee to the Sponsor

DR. RAUFMAN: Thank you. We will now ask if the committee has questions for the sponsor. Please wait to be recognized by the chair before you ask your question.

Yes, please?

DR. JOAD: Actually, I have three questions. I don't know if I get to ask them all. My first question has to do with the data that we know from other clinical studies about -- I'm concerned about comparing with the CF registry. What do we know between real world taking of medicines and socioeconomic status and adherence compared with patients who are on a study, which I understand to be much more adherent and maybe higher socioeconomic status?

So I think there's literature on that and if you could address that.

My second question is I'm concerned about there's no addressing of children under 2, which is, certainly, in pediatric CF clinics, we're dosing them.

My third question was did you compare the side effects with liver enzymes and bilirubin with the same patients that you used when you did do the CF registry? That's all my questions.

DR. BRETTMAN: Okay. So I'll address the second question first about dosing in children under 2. And we feel that additional study is necessary before recommending dosing in children under 2 because of potential leakier guts in young children and so forth.

I'm going to ask Dr. Borowitz to address your first question and Dr. Stevens to address your third question.

DR. BOROWITZ: I appreciate your thinking about patients who represent a range of socioeconomic status, because there is a very clear association between socioeconomic status and outcome in patients with CF.

The registry data was a post hoc analysis, but that represents, if you will, effectiveness of porcine enzymes. All those patients are taking porcine enzymes. I will point out we don't know what the CFA is for any of those patients. CFA is not done for the overwhelming majority of patients in clinical practice.

Our comparison of patients is, in essence, an effectiveness study. It is true that they were enrolled in a protocol, and early on we were following patients fairly closely because of our safety concerns; especially as principal investigator, that's my primary responsibility. But through the latter half of that study, follow-up was done, in essence, about at the same frequency as the standard CF care visits.

So I believe they are comparable, and we had no exclusions based on socioeconomic status. So I believe those two datasets are relatively comparable, even though it is a weak study design and post hoc.

DR. STEVENS: Chris Stevens. I want to just

clarify, your third question was did we look at LFT elevations in the registry in comparison to our data?

DR. JOAD: Right. You had already identified those patients, and I would have thought you would have looked at the safety, as well as the efficacy.

DR. STEVENS: Exactly. Definitely, we wanted to do that, but in the registry, they only collect whether liver function tests were drawn. They don't actually report the actual values of the liver function tests. So that data was not available for that comparison.

DR. BRETTMAN: I'm also going to ask Dr. Durie to comment on this.

DR. DURIE: I should introduce myself first. I'm Peter Durie. I'm a senior scientist at the Hospital for Sick Children and professor at the University of Toronto. I have had an interest in CF for over 30 years. I and a group in Toronto helped to understand the pathophysiology of the pancreas in CF back in the 1970s and '80s, and,

subsequent to that, have been very interested in genotype/phenotype relations in the pancreas and other organs, and in modified genes effects in CF heterogeneity.

I am a paid consultant to, originally, Altus and subsequently to Alnara and have been involved in the development of this program since its onset.

In view of the fact that there are no data in the CF registry, we decided to look at the data in the Toronto CF database. This is a large clinic, and we have been following biochemical measurements in a database that goes back to 1972.

So what I would like to illustrate are some of the data that we've derived from this registry where AST and alkaline phosphatase measurements were taken many years ago and, more recently, ALT measurements have been done. So I'm going to focus on those two measurements, because they have existed in the database for a much longer period of time.

Just show me slide number 164 first. This is a somewhat complicated looking slide, and it's

there deliberately to show you exactly what happens if you measure LFTs on an annual basis over time according to age, in other words, during progression, in individuals with cystic fibrosis. And what you'll see here are marked fluctuations in AST measurements. This is reflected also by ALT measurements and alkaline phosphatase measurements.

Could you also show me slide 169? This is cross-sectional data in a group of 532 patients, in other words, a measurement that was taken at a point in time as part of their routine assessment. And as you can see, there is a difference between patients who have exocrine pancreatic insufficiency who are receiving porcine pancreatic enzymes and individuals that are pancreatic sufficient who are not receiving pancreatic enzymes.

As you can see, that if you look at AST or ALP, or the combination of that, in a single measurement cross-sectionally across the population, almost half the patients had an abnormal measurement. In contrast, the pancreatic sufficient patients are much less; around about 20

percent had an abnormal measurement.

I think that's all I'll show at this point.

DR. RAUFMAN: Thank you.

Dr. Hubbard, I think, had a question.

DR. R. HUBBARD: Yes. Thank you. I have three, I think, simple questions. The first one was, could you expand a little bit on the difference between the formulation used in the long-term studies and in the Phase 2 dose ranging study? I know that you began your presentation with that, but it's not clear to me exactly what the difference was. Is it minor or is it something other than that?

Then my second question has to do with clarifying the ex-U.S. versus U.S. patients. Did they all adhere to the same protocol in every way? And if so, then how do you explain the difference in treatment?

Then my third question had to do with something you mentioned about having a responder analysis for patients who had CFAs that exceeded, I believe, 80 percent or something like that. Do you

have a slide which shows that information that you could share with us?

DR. BRETTMAN: The multiple questions are straining my memory just a little bit. So I want to make sure I can clarify them. So the first question is about formulation. The second one was about whether the adherence to the protocol was the same.

DR. R. HUBBARD: Same protocol.

DR. BRETTMAN: Yes. Yes, exactly. Exactly the same protocol. And, I'm sorry, the third question? I just want to make sure I understand this.

DR. R. HUBBARD: (Off microphone) responder analysis.

DR. BRETTMAN: No, no. I didn't actually refer to a -- I don't believe I referred to a responder analysis in my presentation. Is there a slide in particular that you're thinking of where I made that point?

DR. R. HUBBARD: (Off microphone.)

DR. RAUFMAN: Please use the microphone.

DR. R. HUBBARD: I think it came in around slide 85.

DR. BRETTMAN: Okay, yes. Slide up, please.

Yes. What I was talking about here is I was talking about the patient selection and study design for the porcine products that the FDA has drawn comparisons to with regard to the liprotamase data.

What I mean by responder studies is for one of those products, subjects were put on that product, and after a period of time, I don't remember exactly the timeframe, a CFA was measured while they were on that product. And then before randomization was allowed, they had to demonstrate a CFA greater than 80 percent before they could be randomized. So this is a highly selected population of patients that had the most favorable CFA results. Those were the subjects studied in that study.

Did that answer your question?

DR. R. HUBBARD: Yes.

DR. BRETTMAN: Thank you. I'm going to ask

Dr. Burstyn to address the question about formulation.

DR. BURSTYN: So in terms of the formulation, the formulations were comparable. Could I have the slide up, please?

So within the Phase 2 study, actually, two capsule strengths were used, a 6,500 unit and a 26,000 unit, and the reason this was done was to ensure blinding of the study.

So as you recall, we had three different doses, 6,500, 32,500, and the 130,000. And so it was really a combination of the size 5/size 2 capsules, along with corresponding placebo that would allow us to dose up.

So, for instance, a patient in the highest dose group would have received four actives of the size 2 capsule and one placebo. So it was strictly for blinding purposes.

As you can see, the combination in terms of the mid-dose group received both a size 5 and size 2 active capsule along with the relevant placebo capsules, and the total dosage unit is exactly the

same as that in the Phase 3 study.

The real difference between these two is in the highlighted blue area, which is the diluent, which is a diluent which is essentially a filler, and it's a filler in order to fill up the capsule to ensure there's no space in terms of shaking, because the total amounts filled were 7,500 mgs versus 200,000 mgs. In Phase 3, the total volume of the capsule, and this is the commercial capsule, is the 200 mgs.

DR. RAUFMAN: Thank you. Bear with me. There are a number of questioners and I think I have people in reasonable order. So we'll get to everybody. Dr. Fogel?

DR. FOGEL: Thank you. I have two questions. One is a methodologic question regarding the coefficient of fat absorption. When we used to do these tests using carmine red, one of the questions always was when did the stool actually change color.

My first question is, how did you know when the stool actually turned blue? Because it doesn't

turn a navy blue, at least as far as I understand it; it's usually subtle. And I'm curious as to whether you had any parameters to determine when to start stool collection and when to stop.

The second question regarding the CFA is, did you do dietary evaluations to make sure that the patients actually took a 100-gram fat diet for each of the days?

My second question has to do with slide 50, and I can ask that after I get the answers to the first question.

DR. BRETTMAN: I'm going to ask Dr. Borowitz to address that question.

DR. BOROWITZ: I find it hard to believe that my career has brought me to the place where I'm an expert on stool markers. But we actually used an FD&C blue number 2 for this study, and we used it because when talking to nurses in clinical research centers that had done studies, previous studies of porcine enzymes, they told us that the carmine red was very difficult to see. And CFA is an odious test. Nobody likes to do it. And if the

stool maybe sort of looked red, they would say, "Okay, maybe that's red."

So we sought a different marker. FD&C blue number 2 is approved for both oral and actually intravenous use. We did some dose ranging studies to come up with a 500 milligram amount, which does look blue or green, as it is.

So the way these studies were done is that the first stool that appeared blue or green was discarded. The collection began for every stool thereafter until the last stool that appeared blue or green, which was included in the collection. We did a study to make sure that FD&C blue number 2 did not affect either CFA or the analysis of fat or the analysis of nitrogen.

In terms of the diet for the TC-2A study, subjects were given a 100-gram fat of diet that was planned with the research dietitian. In the 726 study, we actually took that to another level, and subjects ate the identical foods during the first and the second collections. So not only was it 100 grams of fat, but they were identical foods.

DR. FOGEL: And they ate the entire diet. That was documented.

DR. BOROWITZ: Yes. These were done with a dietitian who then looked at the trace, measured the trace afterwards, and then calculated out the amount of fat.

DR. FOGEL: My second question had to do with slide 50. This is Study 726, the outline. It looks like there's variation in the duration of treatment anywhere from 21 to 31 days. Can you just explain why that exists?

DR. BRETTMAN: I'm going to ask Dr. Borowitz to answer that one, as well.

DR. BOROWITZ: As you might imagine, it's very difficult to approach individuals with cystic fibrosis and ask them to be in a study where they need to be in a research center 24 hours a day during this period of time. And so that just allowed for some flexibility in people's lives, and that was the reason for the variation.

DR. RAUFMAN: Dr. Krist?

DR. KRIST: Thank you. I have two

questions, as well, and I'll do the same thing and start with the first one. I'm trying to really understand the statement that the patients in the liprotamase studies were sicker than the patients in the other porcine enzyme studies. And I appreciate slide 85, which showed the differences in the study.

I was wondering if you had any data about the baseline characteristics of patients in the liprotamase studies versus the porcine enzyme studies, somewhat similar to slide 52, that might list body mass index and other characteristics.

DR. BRETTMAN: Unfortunately, that data is not available that we can find. I'm sure it exists somewhere, but it does not appear to be in any of the publications, with some exceptions. There may be a BMI, an average BMI for the overall population, but it's not a Z score. So it's hard to know because we don't know the age distribution of what the BMI actually means.

If you could just put this slide up, please?

So this is the 726 demographics. And

perhaps when I went through this slide, I may have passed over it too quickly. But the statement that you refer to that there were sicker patients included in the study, in part, rests on that bottom line, where the "nutritionally compromised" with the asterisk is.

The definition down below is a BMI of less than 20 kilograms per meter square or less than the 25th percentile. That was a criterion that was used to exclude subjects from one of the studies that's in the FDA table. And by that definition, close to 40 percent of our subjects were nutritionally compromised.

So that's a very substantial difference in the patient population.

DR. KRIST: Just as a follow-up on that. If I'm understanding right, you're saying that the bottom line represented patients that were excluded in the other porcine?

DR. BRETTMAN: In the study -- I don't want to say all of them, because in some of them, the study methods aren't well enough defined to

actually determine that. But in one study where it was well defined -- could you leave that slide up, please?

In the one study where it was well defined, these were the criteria used to exclude subjects. No reason was given, but I think the goal of the porcine PERTs is very different from ours. We're developing a new chemical entity. We need to identify an efficacious starting dose.

Their goal was to -- well, I won't say what their goal was. I shouldn't speak for them.

DR. KRIST: My second question, if that's okay, I was trying to understand the populations in Study TC-2A. And when I looked at Tables 21 and 22 in the FDA papers, it looked like there were more men in arm number one of the study and that there were more patients with a lower CFA in arm number three. And it was a randomized study, so I was just kind of wondering how that happened.

DR. BRETTMAN: It was basically luck of the draw. That's just one of the things that happens in randomization.

DR. RAUFMAN: Thank you. Dr. Lowe?

DR. LOWE: I also have several questions. And I'll do them one at a time, since my memory doesn't work so well either.

I think as most everyone here is aware, the pancreas makes several different lipases that have vastly different substrate specificity. My understanding is that the lipase used here is a neutral lipase. Is that correct?

DR. BRETTMAN: I'm sorry. I didn't hear that.

DR. LOWE: It's a neutral lipase and that it specifically cleaves triglycerides. It doesn't cleave phospholipids or fat soluble vitamin esters or galactolipids.

DR. BRETTMAN: I'm going to ask Dr. Freedman to answer that.

DR. FREEDMAN: So it's a good question. It definitely cleaves triglycerides. Whether it actually cleaves phospholipids is not clear.

DR. LOWE: Someone mentioned that there's no stereoisomer specificity and it cleaves S1, 2 and 3

positions. Do you have any information about fatty acid chain line? In particular, does it cleave very long chain fatty acids?

DR. BURSTYN: There are some in vitro data that shows cleavage of C16, C18 and such.

DR. LOWE: But you haven't done C22 or very long.

DR. FREEDMAN: So we have done in vitro studies. In fact, by GC mass spec, if you look at this lipase, it cleaves all the way at least through 22-6, so through DHA. So it's cleaving long chain fatty acids.

DR. LOWE: The next question has to do with the methodology. So you used 100 grams of fat per day across all age groups and weight groups. So that means that the fat per kilo is going to be much higher in the younger subjects.

Would it have been better to either look at what they're consuming or to normalize it across their weights?

DR. BRETTMAN: Dr. Borowitz?

DR. BOROWITZ: In the youngest subjects, we

used 60 grams of fat per meter square.

DR. LOWE: It also looked like you had a better CFA with acid suppression using your product. Why is that? Do you have an explanation for that, if these are acid soluble, or is there another reason?

DR. BRETTMAN: So I'm going to ask Dr. Borowitz or Dr. Durie to respond to the question about the general impact of acid suppression. It's frequently used in these patients. There is some data in the literature, regardless of the product, that subjects on acid suppression may have higher CFAs. I think it's still controversial whether or not that is true.

We did see differences in subjects treated with acid suppression in terms of the CFA, but, however, in both subjects receiving acid suppression and not receiving acid suppression, both in the short-term study with regard to CFA, the differences were statistically significant.

When we analyzed acid suppression users versus non-acid suppression users in 767, we saw

similar patterns of nutritional maintenance over time.

So that's basically how I'd respond and ask Dr. Borowitz if she has additional comments.

DR. BOROWITZ: There's a certain amount of controversy about use of acid suppression in patients with cystic fibrosis. I think clinicians tend to think of it in terms of the issue of dissolution of enteric coating.

Could I have slide 057 up? This is data unrelated to the development of liprotamase that we generated using a technique called a smart pill. It's a pill that you swallow. It has a pH sensor on it, and we compared individuals with CF to healthy controls that were matched for age, gender and BMI.

Because pancreatic insufficiency affects both high volume bicarbonate rich secretion of the pancreas, as well as the enzymatic secretion, it's not surprising that, in fact, the amount of acid neutralization in the very proximal small bowel is less in individuals with CF than you might expect.

You can see those dotted lines that are the levels of pH that are needed for dissolution of pancreatic enzymes; and so this is the rationale why people often give proton pump inhibitors or H-2 blockers.

But, in addition, there are other issues about an acid small bowel. There's increased precipitation of bile salts. And so there are some reasons, I believe, to think that an acid-resistant lipase would be more useful for patients with CF, but it can't fix the problem that there is an issue with acid neutralization. And so excess precipitation of bile salts might be a reason for fat malabsorption unrelated to exocrine pancreatic insufficiency.

DR. DURIE: I just wanted to add a simple point to what Dr. Borowitz said. Those of us who are caregivers know that patients with cystic fibrosis suffer a lot from gastroesophageal reflux and esophagitis. And so often the indications or the reason why a patient is on acid suppression may have nothing to do with their enzymes.

DR. RAUFMAN: Dr. Shih?

DR. LOWE: I guess another potential explanation is the effect of pepsin on your enzyme preparation in the stomach and that it may be less active at higher pHs.

One last question. Is that okay? I was sort of interested in the long-term study -- actually, there's two questions, I'm sorry -- in the long-term study, where you looked at the Eastern European sites, and you were able to maintain their BMI, but treatment didn't result in improvement.

I'm sure there are many issues that could explain that. Do you have your theories as to why you didn't see improvement in their nutritional status?

DR. BRETTMAN: Well, I'm going to again ask Dr. Borowitz to answer this question, but I'll start by saying that at baseline, they were severely nutritionally compromised while taking porcine enzymes. So guessing, there are a number of factors why they were there and why they may not

get better in spite of optimal therapy.

But I'll ask Dr. Borowitz if she has any additional comments on that one.

DR. BOROWITZ: If you want to stay data-driven, what we can show you is what we've shown you. If I step away from the data, I can speculate about the reason. But is that what you're looking for, speculation as opposed to data?

[Non-verbal response by Dr. Lowe.]

DR. BOROWITZ: I do believe that there was a certain amount of selection bias for people who were in worse shape to be in this study, and there may have been a certain sense of desperate need to use this drug, and that's certainly a possible explanation.

There are differences in diet that we looked into in other countries, but we don't have a real explanation for that finding. The main reason to show you that data is that it is striking that that one subgroup really drives the overall data. And I think when we think about this drug in the context of what I consider to be modern CF care, as I've

stated, I want to see this drug as an option for patients with cystic fibrosis, and I think it's important to separate out the data into those groups.

DR. BRETTMAN: Excuse me a minute. I'd just like to confer with Dr. Borowitz for a minute.

[Pause.]

DR. BRETTMAN: The other point, I think, in looking at this data is when you see a slope of zero, you're somehow not happy with that because you expect to see things get better. But the reality is, as Dr. Borowitz showed you in that BMI percentile curve from the Cystic Fibrosis Foundation, over time, particularly in the young ages, they go in the other direction in spite of standard of care therapy.

So maintaining nutrition in a group of subjects who were so nutritionally compromised at baseline, I think is very strong evidence of the clinical benefit of liprotamase.

DR. LOWE: That's a very different time frame.

DR. RAUFMAN: In the interest of time, I'd like to move on and allow additional people to ask questions. I also ask that you please focus your questions and please focus the answers so that we keep things reasonably short.

Dr. Shih?

DR. SHIH: This is a question about the BMI, the long-term study of 767, as well. Based on your presentation, you concluded that there's maintenance of the BMI, and there's an early drop and then stabilized. Right? But you used a method called the last observation carried forward approach.

Now, that may prevent the further dip, and I do not know and that's my question, because you have about 32 percent of early withdrawal. And you also say that they all occurred early in the study, that they withdraw from the study in the early time.

So the question is, do you have other analyses that will give a sensitivity for this last observation carried forward approach?

DR. BRETTMAN: Yes, we do. And if I could have the slide on, please. So a number of other analyses were done, and I can ask Dr. Campion to comment further on this, but we did a worst observation carried forward, as well; so that the worst observation at any time on study was carried forward.

Unfortunately, you can't tell that they're different lines, because they are superimposable. So that's at least one other way we looked at it to try to address the concern you raise.

DR. SHIH: No, no, no. When you say the worst observation carried forward, the worst observation may just be the last observation.

DR. BRETTMAN: Yes.

DR. SHIH: So that's why they superimpose.

DR. BRETTMAN: Yes, I understand.

DR. SHIH: But I would like to ask another analysis than carry forward anything.

DR. BRETTMAN: Dr. Campion?

MS. CAMPION: I'm Marilyn Campion. I'm a biostatistics consultant for Alnara. I'd like to

explain what we did with the worst observation carried forward, which was up to the time of a subject withdrawing from treatment, I searched for their worst value on treatment and carried that observation forward, which is what you saw in the picture.

About a third of the time, the observation that was the worst observation was actually not the last observation that we observed. So a third of the times, if we were to carry the worst observation forward, we would have actually carried the better observation, because the subjects were going down and then they were coming back up.

One other observation that we did make is that the subjects who withdrew early were actually subjects who, on average, had a higher Z score at baseline, and the speculation there being that those subjects perhaps felt that they didn't need the treatment as much has other subjects did and, therefore, didn't want to put up with the rigors of the study, which were really quite extensive for a year-long study to record on a daily basis, five or

more times a day, when you took capsules, how many you took capsules. So we had a lot of early dropouts for patients who were actually not as severely compromised.

Does that answer your question?

DR. SHIH: I was looking for some other method than the observation carried forward, and there are other methods. And you know that the FDA recently had a panel studying the missing data, and they have the report from the expert group. And I was hoping that you had done other analyses, like not carry forward any data, just let it be missing, and then using some more statistical approach to address the question.

MS. CAMPION: So we have summarized the data based upon observed cases only, but we've done no specific analyses where we've done other observations carried forward.

DR. RAUFMAN: Thank you. We can maybe address this again later if necessary. Dr. Hasler?

DR. HASLER: Thank you. I have questions in three areas. The first one relates to your primary

endpoint, the improvement in CFA. And as an adult gastroenterologist, I don't use that parameter, but we do measure fecal fats.

Let me just make sure I have this correct. So if you have a person with severe pancreatic insufficiency who puts out 50 grams of fat a day and you get a typical 20 percent improvement in CFA, does that mean their fecal fat improves to 40 grams a day? That's my first question related to that.

The second question relating to the CFA is a number of your speakers this morning used almost a cutoff of 80 percent CFA as being a person with mild versus uncontrolled pancreatic insufficiency. I didn't see in any of the slides presented what percentage of your patients actually exceeded 80 percent on therapy.

So that's my first series of questions, if you want to comment on that.

DR. BRETTMAN: So the first question is the CFA is an absolute percent. So it's not a percentage change of the percentage.

Did that answer your question?

DR. HASLER: Well, I'd like to know what sort of a typical improvement in fecal fat did you see, for example.

DR. BRETTMAN: Okay. So if somebody were -- okay. Let's use 100 grams as the example, since that's what we used in our trial. So subjects were given a diet that contained 100 grams of fat a day. Over a three-day period, that would be 300 grams.

The stool, marker-to-marker, for that period of time was collected, and an analysis of the fat remaining in the stool was done. So if, at baseline, let's say, 20 grams or 20 percent of that 100-gram diet or 60 grams over a three-day period was still in the stool, then that would be a baseline CFA of 20. If they then went on treatment and now there was only 10 grams per day of fat, that would be a CFA of 90 percent.

DR. HASLER: So it would go from 80 to 90.

DR. BRETTMAN: Yes.

So your second question was how many of the

subjects achieved a CFA of greater than 80 on treatment.

DR. HASLER: That's correct.

DR. BRETTMAN: Okay. Just a moment while we call up the slide. We have that data.

I'm wondering if we can maybe move on to the next question and look for that when we come back.

DR. HASLER: My second question is one -- and one of the other questioners asked about other confounders, and I see a number of adult CF patients who have associated severe dysmotility and pancreatic insufficiency.

One of the things we see in adults -- I don't know so much about in kids -- is severe bacterial overgrowth. And I was wondering if liprotamase is degraded by bacterial in the small intestine and if you saw any effects one way or the other of concomitant antibiotic therapy.

DR. BRETTMAN: Dr. Borowitz, would you like to answer that?

DR. BOROWITZ: So we did not have any specific measure of bacterial overgrowth. And you

are correct, there is a wide range of confounders. And although CFA is the surrogate endpoint that we used in these studies, you're absolutely right; it is confounded by a wide variety of things. And I think that's why some of this data is confusing.

But the range of confounders is quite wide, and we did not specifically look at a test to measure that. And, as you know, there's controversy over whether breath testing is, in fact, the best way to look for bacterial overgrowth.

DR. HASLER: And my final question, while you're coming up with your data, is did you look at pain as a secondary endpoint. We see that in a lot of our adult chronic pancreatitis and a lot of use enzymes to try and reduce pain, in addition to steatorrhea, and I was wondering of those benefits exist.

DR. BRETTMAN: Dr. Freedman?

DR. FREEDMAN: I agree, it's a wonderful question. I think Dr. Stevens had shown you about abdominal pain related perhaps to steatorrhea. I

can give you anecdotes. One of the things is as --

DR. RAUFMAN: I ask that you please focus your answer.

DR. FREEDMAN: So I think one of the things that we're focused on is more the insufficiency symptoms, and so that's really what we have data on.

DR. RAUFMAN: And is there a response to Dr. Hasler's second question?

DR. BURSTYN: I'm sorry. Can you repeat the second question?

DR. HASLER: What percentage of patients exceeded 80 percent CFA on treatment?

DR. BURSTYN: I think we may be ready.

DR. BRETTMAN: Unfortunately, I know we have the slide, but I can't lay my hands on it right now. So in the TC-2A study -- and this is from memory, I think these numbers will be close, but I will confirm to make sure I'm giving you accurate information; that in the TC-2A study, approximately 20-plus percent achieved a CFA greater than 80 in that mid-dose group. And in the 726 study, it was

approximately 17 percent.

When you look at the less than 40 population in the 726 study, 33 percent achieved a CFA of greater than 80 percent. And I believe those numbers are reasonably accurate, but if I misstated, I will come and clarify that.

DR. RAUFMAN: To keep us on schedule, I'm going to move ahead with the break. I know that there are a couple of people on the committee that had questions, and we'll find time for those later on. So please keep your questions.

So we'll now take a 15-minute break. We will reconvene again in this room in 15 minutes from now at 10:40 a.m. Thank you.

(Whereupon, a recess was taken.)

DR. RAUFMAN: I'd like to call the meeting back to order, please. Before we start with the FDA presentation, we have a quick response to Dr. Hasler's question.

DR. BRETTMAN: Thank you. So it turns out we don't have a slide, but I have the data. So in the TC-2A study, which was done in the United

States, 28 percent greater than 80; and in the 726 study in the United States, it was 17 percent.

DR. RAUFMAN: Thank you. And we'll now proceed with the FDA presentations.

FDA Presentation - Marjorie Dannis

DR. DANNIS: Good morning, and thank you everyone who braved the elements to get here today. My name is Marjorie Dannis, and I'll be the first and the last of the speakers for the FDA presentations.

Here is a brief overview of the upcoming presentations. First, I'll begin with some background information. Next will be a presentation on chemistry, manufacturing and controls. Following that will be a brief presentation on clinical pharmacology. And then I'll return to discuss our view of the efficacy and safety of liprotamase.

Liprotamase is the first biotechnology product for the treatment of exocrine pancreatic insufficiency, or EPI. All of the others are porcine-derived pancreatic enzyme products, or

PEPs.

Liprotamase contains only microbially-derived enzymes, crystallized cross-linked lipase, crystallized protease, and amorphous amylase. It is available in one capsule strength with the lipase, protease and amylase shown here. You'll hear more specifics about the drug product in the CMC presentation.

The applicant's proposed indication is for the treatment of patients with exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions. Later, I'll provide an overview of the approach we have used for porcine-derived pancreatic enzyme products to grant these efficacy claims.

The applicant has proposed starting and maximum doses in the age categories shown. The proposed dose ranges do not exceed the maximum doses recommended in the CFF guidelines. The applicant proposes that for patients less than 7 years old, the liprotamase water suspension should be swallowed directly or mixed in soft acidic

foods.

The clinical pharmacology reviewer will discuss the liprotamase water suspension. It should be noted that the youngest patient in the liprotamase studies was 7 years old.

Now, the regulatory history. The division stated in several pre-submission meetings that an increase of 10 percent in mean coefficient of fat absorption, or CFA, over the placebo group is not sufficient to provide a clinically meaningful improvement in fat malabsorption, particularly in those with severe fat malabsorption at baseline.

In those patients who have a low baseline CFA, an increase of 30 percent in mean CFA would be considered clinically meaningful. In numerous meetings, low baseline CFA was described as baseline CFA less than 40 percent.

The division agreed with a minimum exposure of 200 patients for six months and 100 patients for one year. The division clarified that the pancreatic enzyme product, or PEP, guidance applied to porcine-derived PEPs and not liprotamase.

The division stated, in general, two adequate and well controlled studies are required to support an indication for the intended population. However, a single trial may be acceptable if the evidence presented is highly persuasive statistically and the observed outcomes are consistent across study subsets. This is the agency's standard recommendation based on the evidence of effectiveness guidance.

Now, a discussion of porcine-related PEP approvals. Key to the approval of each PEP was the agency's longstanding determination that replacement of pancreatic enzymes has clinical benefits for patients with EPI. There is a large body of evidence in the literature that supports the efficacy and safety of PEPs.

In light of this evidence, only a short-term demonstration of efficacy and safety of that particular PEP to be marketed was required to support its NDA approval.

The body of evidence in the literature allowed each porcine-derived PEP to receive a

general indication for EPI, regardless of whether only CF patients were studied in the short-term trial for that PEP. For each of the approved PEPs, a short-term trial in patients with EPI due to CP supported an approved indication that specifically states "exocrine pancreatic insufficiency due to cystic fibrosis or other conditions."

Note that the applicant for liprotamase is proposing specific indication language for chronic pancreatitis or pancreatectomy, but has primarily studied CF patients and has conducted only an open label chronic pancreatitis study that was terminated early and enrolled 13 patients, most of whom did not complete the study.

The safety and efficacy of PEPs in pediatric patients has been described in the medical literature and through clinical experience. This allowed each PEP to be indicated for all age groups, regardless of whether patients in these subpopulations were included in the short-term trial for that particular PEP.

This concludes the background section of my

presentation. The next speaker will be Dr. Lacana, who will discuss chemistry, manufacturing and controls.

FDA Presentation - Emanuela Lacana

DR. LACANA: Good morning. My name is Emanuela Lacana and I am the team leader for the quality group responsible for the review of the chemistry, manufacturing and control section of this new drug application. The review team is listed in this slide and included Howard Anderson, Juhong Liu, Nikolay Spirdonov, and Wei Guo.

This submission was more complicated and extensive than other submissions we have reviewed in the past, given that three separate purified drug substances obtained via biotechnology processes were manufactured and finally combined into a solid dosage form.

The commercial scale drug substances were manufactured at Lonza, a contract manufacturer, while the drug product was manufactured at a second drug contract manufacturer.

The submission included additional

facilities related to laboratories used as testing sites and warehouse for storage. Many of these facilities have been inspected by the FDA, and Dr. Anderson participated in the inspection of the Lonza manufacturing site.

Liprotamase is a drug product in solid dosage form, filled into capsules. The enzymes in specific ratios are formulated with pharmaceutical excipients designed to ensure homogeneity and adequate dissolution of the product after disintegration of the capsule.

Next, I will provide a very brief description of the three individual enzymes. The description is brief, because they have already been described in detail by the applicant, and this will be only a quick reminder.

Lipase is an enzyme of microbial origin, produced by a recombinant DNA technology, and is active in the pH 5 to 9 range. The lipase can hydrologize triglycerides into fatty acid, mono and diglycerides, as depicted in the figure on the left. The enzyme is purified, crystallized and

cross-linked to prevent proteolytic degradation.

The protease is a non-recombinant enzyme produced by fermentation. It is a serum protease, meaning that serum is one of the amino acids that is part of the catalytic site, has an optimal activity of pH 8, and has a broad specificity in that it can cleave polypeptides into the single constituent amino acids. Similarly to the lipase, the protease is crystallized to increase stability.

Amylase hydrolyzes long-chain sugars into the constituent monosaccharides and has an optimal pH range between 4.5 and 6.5. Similarly to the protease, amylase is also a non-recombinant protein and is produced by fermentation. The enzyme is purified and is dried into an amorphous powder.

As is common for product development of many therapeutic proteins, manufacturing changes were introduced in the drug substance and drug product manufacturing process and the result of the studies conducted to evaluate whether drug substances prior to formulation into capsules -- that was the subject of the slide provided by the

applicant -- were physically chemically similar following these changes, were submitted in the application and we reviewed it.

Our evaluation of these results is that following changes in the manufacturing process of the Phase 3 and Phase 1/2 material, these materials were significantly different in a number of critical quality attributes; and with this, I mean quality attributes that are linked to clinical performance.

The significance of these differences from a clinical perspective could not be evaluated. Therefore, we concluded that the clinical safety and efficacy cannot be directly compared in the studies that were conducted using the two different products.

Regarding the commercial material, the to-be-marketed product, the data is still under review, but our preliminary evaluation is that minor changes were observed in critical quality attributes. These changes are unlikely to have an effect on clinical performance.

The liprotamase drug product contains three enzymes combined with standard pharmaceutical excipients. The enzymes are mixed in specific proportion based on their enzymatic activities, listed in this slide.

Lipase activity, in this slide, is listed in tributyrin units. USP assay units were used throughout the clinical trial, and the difference between the two measurements relates to the type of substrate using the enzyme reduction.

While the USP assay uses olive oil as a substrate, tributyrin is a synthetic substrate containing shorter fatty acid chains. The applicant proposed a correlation between the two assays, but we need more data to confirm that the correlation indeed exists.

Liprotamase has been designed to replace the enzyme produced by the pancreas and allow for food digestion. The current treatment available for enzyme pancreatic insufficiency consists of replacement therapy with porcine-derived pancreatic enzyme products, or PEPs.

Now, there are a few salient characteristics of liprotamase and PEPs that I would like to highlight and compare. Liprotamase consists of three purified microbial enzymes. These enzymes have not evolved to digest food, while the PEPs are a complex mixture of multiple enzymes, some of which are still uncharacterized.

Only one of the enzymes in liprotamase will be active in each major class of macromolecules, namely, proteins, carbohydrates, or fatty acids, while the PEPs, which contain enzymes representing the full pancreatic output, are likely to have multiple enzymes capable of acting on different components of each major macromolecule class. One example is phospholipase-A that can digest phospholipids. Therefore, it may be biologically plausible that PEPs might be more efficient at digesting food.

Liprotamase enzymes are of a microbial origin and are obtained by fermentation in the absence of animal-derived materials. Therefore, the risk of contamination with viral agents is

negligible.

Further, PEPs, due to the nature of the source material, some porcine virus may be present in PEPs preparation, and there could be a theoretical risk that these viruses may cross species and infect humans.

The topic was the subject of an advisory committee meeting in 2008 that agreed with the conclusion that the risk was indeed theoretical and recommended that information to this effect was provided to patients and health care providers.

We could also have a theoretical supply issue with PEPs if a new emerging epidemic occurs in the pig population. The risk of such an occurrence is negligible for liprotamase. However, supply issues could not be excluded due to other potential contaminations or manufacturing issues.

Another characteristic of liprotamase is that the lipase used in the drug product is independent of colipase, which is not necessary to reach maximal enzyme activity. In contrast, the triglyceride lipase present in the PEPs does

require colipase to reach maximum activity. However, we had asked the PEPs manufacturers -- the PEPs applicants to conduct studies aimed at evaluating colipase content in PEPs, and the data resulting from these studies demonstrated that colipase is always in excess in PEPs and, therefore, it is not a limiting factor for lipase activity.

With this, I conclude my presentation and I leave the podium to my colleague, Dr. Lin Zhou.

FDA Presentation - Lin Zhou

DR. ZHOU: Good morning, everyone. My name is Lin Zhou. I am the primary clinical pharmacology reviewer for this NDA. Dr. Hae Ahn and Dr. Gil Burckart are the secondary reviewers for this NDA.

The topics I'm going to present today are, first, the stability of liprotamase in water and soft acidic foods; second, the proposed use of liprotamase in G-tube feedings.

For patients who are unable to swallow an intact capsule or taking less than a full capsule,

the applicant proposed to open the capsule and mix the contents of the capsule with water and soft acidic foods for administration. So far, the applicant has tested the stability of liprotamase in water, apple juice, applesauce, and yogurt.

Now, I'm going to briefly describe how the experiments were performed. Capsules were opened and the contents of the capsule were mixed with the test matrix. The activity of enzymes was measured upon mixing, at 15, 30, 60, and 120 minutes with tributyrin assay for lipase and modified USP assays for protease and amylase.

Now, let's look at the data. This slide shows the stability of lipase in different matrices. The Y-axis is the mean remaining activity shown as percent of control. Control is the enzyme activity measured upon initial mixing.

As shown in the figure, at 15 minutes, the activity of lipase in different matrices ranged from 94 to 108 percent of the control and showed a progressive decrease to 50 -- to 70 percent activity or unchanged over two hours.

There appears to be a reciprocal relationship between the stability of lipase and the pH value of the matrix. The higher the pH value, the lower the stability.

In contrast, the activities of protease and amylase remained unchanged over two-hour periods in all matrices tested.

One thing I would like to point out here is the assays used for determining the activity of lipase, protease and amylase have not been validated for different matrices. Validation data are still pending.

Provided that the assays were validated, when liprotamase is mixed with water or soft acidic food up to pH 6.5, each enzyme retained greater than 90 percent of the activity within 15 minutes.

Next, I would like to talk about the applicant's proposed use of liprotamase in G-tube feedings. According to the applicant, about 11 percent of patients in the CF Foundation registry rely on the nighttime gastrostomy tube feeding of dense medical fluid for adequate

nutrition and weight gain. Because liprotamase is in powder form and is not enteric coated, the applicant is proposing to use liprotamase in G-tube feedings. The applicant is proposing to administer liprotamase to the gastrostomy bag, mix it with enteral formula, and infuse the mixture into the stomach overnight via the G-tube.

In the proposed labeling, the applicant provides a detailed description on how to administer liprotamase to patients on G-tube feedings. Their rationale for the proposed use as stated in the briefing background package is that the addition of liprotamase to an enteral formula resulted in delivery of free fatty acids, peptides, and amino acids ready for absorption without the need for further digestion. However, there are no safety or efficacy studies to support this claim.

Although we're deliberating on this, this slide lists data required for labeling the proposed use at this time. The stability of liprotamase enzymes in formula over time needs to be measured with adequate assays. The suitability of

individual formulas would have to be studied. Mainly, the possibility of individual formulas needs to be tested.

The applicant so far has tested four brands of formula. Two of them became viscous when missed with liprotamase and are not suitable for the G-tube feeding. The issue of the leaching of materials from the gastrostomy bag must be addressed in the presence of liprotamase.

Last, but not the least, the efficacy of liprotamase administered as an infusion with the intent of pre-digestion would have to be studied in a clinical trial, the reason being enteral formulas are a complex mixture of fats, proteins, carbohydrates, vitamins, trace elements. And we have no standard for what pre-digestion should result in, therefore, to demonstrate efficacy, we have to rely on either the clinical parameters, which is growth at a nutritionist or the efficacy surrogate marker, which is CFA.

To conclude what I have presented, provided that the assays are validated, when liprotamase is

mixed with water or soft acidic food up to pH 6.5, each enzyme retained greater than 90 percent of the activity within 15 minutes. Regarding the proposed use of liprotamase in the G-tube feedings, the applicant's data are not sufficient for labeling such use. Additional studies, including clinical trials, will be needed.

Now, I would like to invite Dr. Dannis back to the podium.

FDA Presentation - Marjorie Dannis

DR. DANNIS: Now, I'll be presenting our review of the efficacy and safety of liprotamase. The applicant has provided much of the background information regarding efficacy and safety. We thought it would be most helpful to the committee if we gave you our view of the efficacy and safety and filled in some information where appropriate.

First, I'm going to speak about the basic design and main efficacy results of the pivotal study, Study 726. I'll also discuss our view of the dose ranging trial, Study TC-2A. Then I'll discuss the long-term trials. I'll primarily

discuss Study 767 in CF patients, and I'll talk about the group-matched external control study that the applicant has chosen. I'll also include, where relevant, discussion of Study 810, a study conducted in a small number of pancreatitis or pancreatectomy patients, which was terminated early.

Next, I'll discuss our view of the major safety concerns, the potential risk of fibrosing colonopathy and the potential for inadequate growth and malnutrition in pediatric patients, as well as other safety issues, the observed transaminase elevations and the cases of distal intestinal obstruction syndrome, which occurred during these studies.

My goal is to allow you to consider liprotamase's risk-benefit profile more fully as you consider the questions we have posed to you.

First, efficacy in the short-term trials. The major efficacy study was the pivotal study, Study 726. This was a multicenter, randomized, double-blind, placebo-controlled study in patients

with EPI due to CF. Patients were at least 7 years of age; 138 patients were randomized. It should be noted that patients with baseline CFA levels greater than 80 percent were excluded from randomization.

The study design is shown by study periods and the treatment during that period. Following the screening period where patients were on their usual PEP, patients entered the inpatient off-enzyme baseline period for about a week. CFA was measured during that time.

Then patients entered the open label treatment period for about three weeks. This was followed by an inpatient, double-blind treatment period for about a week. Here, patients were randomized to liprotamase or placebo. CFA was measured once again.

The diet was a 72-hour, controlled, 100 gram per day high fat diet during inpatient stays only. The dose was one capsule of liprotamase with each of three meals and two snacks, or five capsules per day. Note that there was a fixed dose. The dose

was not individually titrated per patient.

The change in CFA, in other words, CFA during double-blind treatment period minus CFA during baseline period, was determined. The primary endpoint was the difference in the change in CFA between the liprotamase and treatment groups. The primary efficacy analysis was in patients with baseline CFA less than 40 percent. The formula for calculation of CFA is shown. It was determined from an inpatient 72-hour stool collection for fecal fat.

Demographics of the patients are shown here. The characteristics shown -- age, gender and race -- were comparable between treatment groups. No patients less than 7 were enrolled. The total number of pediatric patients ages 7 and older was 64, the number of patients ages 7 to 11 was 28, and the number of patients ages 12 to 16 was 36. As shown here, the baseline values for the liprotamase and placebo groups were similar.

Here are the primary efficacy results. The change in CFA in the baseline CFA less than

40 percent patients, or the primary analysis population, was 20 percent in the liprotamase group and 5 percent in the placebo group. The difference between the two groups was 15 percent. The difference was statistically significant, with a p-value of .001.

The change in CFA in the overall population was 11 percent in the liprotamase group and .2 percent in the placebo group. The difference between the two groups was 11 percent and was statistically significant.

The changing CFA in the baseline CFA greater than or equal to 40 patients was 7 percent in the liprotamase group and negative 2 percent in the placebo group. Thus, the difference between the two groups was 9 percent and was statistically significant.

A secondary endpoint included in the studies of PEPs is the change of coefficient of nitrogen absorption, or CNA. This is a comparison of CNA on treatment with CNA without treatment. CNA is not the basis for determination of efficacy because of

its limitations as a measure of protein absorption.

For example, urine nitrogen is not measured and movement of nitrogen across the bowel wall is also not measured. However, documentation of an increase in CNA supports that proteases present in the PEP are physiologically active. The CNA results shown here support the fact that proteases present in liprotamase are physiologically active.

Now, subgroup analyses. Subgroup analysis by age is shown in the table by categories of baseline CFA. The treatment difference does not appear to be consistent across all age subcategories. The subgroup analysis by age suggested that age 12 to 16 year patients had a numerically lower treatment difference than the other two age groups in the overall baseline CFA category.

The results in the baseline CFA less than 40 subgroup are difficult to interpret because of the small number of patients in the pediatric age categories by treatment arm. Individual results for the pediatric patients were shown in the

briefing document.

Subgroup analysis by country is shown in the table by categories of baseline CFA. The treatment difference does not appear to be consistent by country, and this is U.S. versus non-U.S. sites. The magnitude of the treatment difference is numerically higher in the U.S. sites than in non-U.S. sites across all baseline CFA categories.

Subgroup analysis by concomitant acid suppression is shown in the table by categories of baseline CFA. For the overall baseline CFA category, the treatment difference appears to be comparable for the acid suppression and the non-acid suppression groups. However, the patients who received acid suppression had a numerically higher change in CFA than patients who did not receive assay suppression in both liprotamase and placebo arms.

For the baseline CFA less than 40 category, the treatment difference for the acid suppression group is numerically higher than that of the non-acid suppression group.

These subgroup analyses suggest that treatment difference is not consistent across subsets defined by age, country, and concomitant acid suppression therapy.

Now, a responder analysis. The division has generally accepted that for the most severely affected EPI patients, defined as baseline CFA less than 40 percent, an increase in CFA of at least 30 percent represents a clinically meaningful result.

At the request of the division, the applicant performed a post hoc responder analysis, in which a responder was defined as a patient experiencing an increase in CFA of greater than or equal to 30 percent from baseline. This is summarized in the table by baseline CFA category.

In each of the baseline CFA categories, the active arm had a higher proportion of responders than the corresponding placebo arm. The treatment difference is highest in the baseline CFA less than 40 percent group. This analysis, although post hoc, gives us useful information about clinical

activity.

Now, the other short-term study, the dose ranging study. Although the pivotal study used one fixed dose, the dose ranging study used three fixed doses. Note that neither study used individually titrated doses. The applicant has described the results of the study.

It should be noted that the increase in CFA was not proportional to the increase in dose. The product used in the dose ranging study differs physicochemically from the product used in the pivotal and long-term studies.

Features and results of the dose ranging study will be presented later in the context of individual study designs and change in CFA results.

Now, on to the long-term study in CF patients, Study 767. Study 767 was an open label, long-term safety study in 214 patients ages 7 to 62. It was 12 months in duration and had a single arm, with no control. The dose was five capsules per day.

The protocol allowed for increases to eight

capsules per day for weight loss, inadequate weight gain in pediatric patients, and EPI-related steatorrhea. Greater than eight capsules per day were allowed on a case-by-case basis, but doses were not to exceed the CFF guidelines, which, again, are a maximum of 10,000 units of lipase per kilogram per day. The diet was not standardized.

The applicant performed exploratory analyses in this long-term safety study. Z scores are standard scores used to compare a sample, in this case, the outcome from Study 767, to a standard distribution, in this case, 2,000 CDC growth charts based on the normal population. Note that there was no control arm and there were no protocol-specified efficacy endpoints.

Due to the concern over the apparent lower change in CFA with liprotamase compared to porcine PEPs, we explored this data.

This slide shows mean BMI Z scores for the overall study population. We determined that mean BMI Z scores appeared to decline for the first two to three months and then appeared to stabilize for

the duration of these study, but never appeared to return to baseline. Although not shown here, the same trend was observed with mean Z scores for height and weight.

This slide shows mean Z scores by age subgroups. Mean height, weight, and BMI Z scores appeared to have declined for the patients ages 7 to 11 and 12 to 16, but appeared to be stable for the 17 and older patients. Note that height and weight Z scores are not shown here, but were shown in the briefing document.

This slide shows mean BMI Z scores by region, and this is U.S. sites versus non-U.S. sites. The same trend of initial decline for the first two to three months, followed by stabilization for the duration of the study, was observed in both the U.S. and non-U.S. subgroups.

The U.S. subgroup had numerically higher mean height, weight, and BMI Z scores than the non-U.S. subgroup at each of the visits. Note that only the BMI Z scores are shown here, but the height and weight Z scores were shown in the

briefing document.

This observed difference between the U.S. and non-U.S. subgroup is important in our later discussion of the external control study that was proposed as a comparator after 767 was completed.

The applicant also conducted BMI shift analyses. The applicant defined BMI classifications of acceptable, at-risk and unacceptable are shown in the top table. The applicant's classifications are based on ranges of BMI for patients greater than age 20 and ranges of BMI Z scores for patients ages 7 to 20.

For example, a 30-year-old patient would have a BMI classification of unacceptable if his BMI was 18, at risk if his BMI was 19.5, and acceptable if his BMI was 21.

The applicant's definitions of improvement and worsening are shown in the bottom table. As you can see, worsening is defined as patients going from an acceptable BMI category to at risk or unacceptable. Another option for worsening is an at-risk patient falling to unacceptable.

The BMI shift analyses for the overall population are shown here. The majority of patients had neither worsening nor improvement. As the study progressed, there was a higher proportion of worsening than improvement. Note that of the 214 patients that started, one-third did not complete the study.

This table shows the BMI shift analyses by age subgroups. In each subgroup, once again, the majority had neither improvement nor worsening. In each subgroup, there was a numerically higher proportion of worsening than improvement. Virtually everywhere, there were more worsening than improvements.

The highest proportion of worsening was observed in patients ages 7 to 11 as compared to the other subgroups. The number of patients are not shown here by study visit, but recall that one-third did not complete the study. Note that approximately half of this number withdrew due to adverse events.

This slide shows the patients who

discontinued from Study 767 due to adverse events. The most commonly reported AEs and the associated percentages are listed on the slide. It should be noted that all of these are symptoms of exocrine pancreatic insufficiency.

Now, I'll discuss the group-matched external control study that was proposed as the comparator after Study 767 was completed. The applicant was fortunate to select data from the CFF registry for comparison because the CFF registry captures about 80 percent of CF patients in the United States. The comparisons made between the two studies were descriptive only. No statistical comparisons were made.

The group-matched external control study was a retrospective cohort study of over 5,600 CF patients from the CFF registry. The key selection criteria were patients had to be ages 7 or older, on treatment for EPI with PEPs, and have three or more visits during 2007 to 2008, which was the same time period that Study 767 was conducted.

Methods of the group-matched external

control study. Data were collected at a minimum of baseline, 12 months, and one other visit. Outcomes included Z scores for height, weight, and BMI. Z scores were determined using 2,000 CDC growth charts based on the normal population.

Although matched on age, sex and race, there were many differences between the two groups that made comparisons difficult to interpret. The two studies were not matched on baseline BMI. The BMI Z score was lower in Study 767 than in the group-matched external control study.

The two studies were not matched on country. Approximately half of Study 767 patients were non-U.S. patients. Note that results of the Study 767 suggested numerically lower mean BMI scores in the non-U.S. than U.S. patients. All of the group-matched external control study patients were from the U.S. There may have been other differences between the two studies, such as CF severity and other co-morbidities.

There were differences in study design. Study 767 was a prospective cohort and the group-

matched external control study was a retrospective cohort. These study design differences contributed to differences in the clinic visit schedules.

Visits were fixed in Study 767, yet there was batching of visits in the group-matched external control. By batching, I mean widely disparate schedules were grouped in the group-matched external control study to make the clinic visit intervals more comparable to those of Study 767. For example, in the group-matched external control, week 8 could be anywhere between week 4 and week 10. All of these differences made comparison between these two studies difficult to interpret.

So the limitations of comparisons between Study 767 and group-matched external control study include the external control was not defined in the 767 protocol. There were multiple unplanned exploratory comparisons made. The definition of baseline of Study 767 is week 8 in some of these comparisons.

The applicant's stated rationale was that

eight weeks was required to adjust to liprotamase from prior therapy. This is of concern because mean Z scores for BMI, height, weight appeared to decline for the first eight weeks and then appeared to stabilize; however, did not increase to starting levels.

Additional limitations of the comparisons to the group-matched external control study are shown here. There is limited validity to the comparisons of FEV1 and hospitalization data, because one-third of the Study 767 patients did not complete the study.

Therefore, FEV1 and hospitalization data are unavailable for these particular patients. Thus, interpretation is complicated by the extent of missing data.

We have described the limitations of the comparisons that were made. This slide and the slides that follow show the key principles for comparisons to external controls. These are described in the ICH E10, choice of control group and related issues in clinical trials.

Control patients in the population expected to receive the test drug should be as similar as possible and they should have been treated in a similar setting and in a similar manner, except with respect to the study therapy. Study observations should use timing and methodologies similar to those used in the control patients.

To reduce selection bias, selection of the control group should be made before performing the comparative analyses. Any matching on selection criteria or adjustments made to account for population differences should be specified prior to selection of the control in conformance of the study.

Because blinding and randomization are not available to minimize bias when external controls are used, there are likely to be both identified and unidentified or unmeasurable differences between the treatment and control groups, often favoring treatment.

A consequence of the recognized inability to control bias is that the potential persuasiveness

of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatments than those that would be considered necessary in concurrently controlled trials.

Now, I'll talk about studies of approved PEPs and liprotamase. For your reference only, we have tabulated study design features of the registration trials of the porcine PEPs alongside those of the liprotamase trials.

In the left three columns, selected features of the three approved PEPs, which are Creon, Zenpep and Pancreaze, are shown. In the right four columns, selected design features of the liprotamase dose ranging study, pivotal study, and long-term CF study are shown. The average dose is shown in the first row and whether the dose was titrated individually or fixed is shown in the second row.

Creon used a fixed dose, but unlike the other studies, was based on grams of fat per day.

The dose was 4,000 units per gram of fat per day. This is the upper limit recommended in the CFF guidelines. The average does based on body weight was 11,000 units per kilogram per day. The upper limit recommended in the CF guidelines is 10,000 units per kilogram per day.

Zenpep and Pancreaze were individually titrated to control EPI symptoms. The average dose based on body weight was approximately 6,000 units per kilogram per day for each of the studies.

The short-term liprotamase studies used fixed doses that were not body weight-based. The doses shown here are based on the median body weight. The middle dose arm of the dose ranging study had an average dose of approximately 3,000 units per kilogram per day. The high dose arm of the dose ranging study had an average dose of more than 11,000 units per kilogram per day. Once more, the upper limit recommended by the CFF guidelines is 10,000 units per kilogram per day.

The active arm of the pivotal study had an average dose of approximately 3,000 units per

kilogram per day. The long-term study allowed individual dose titration, and the average dose was about 3,500 units per kilogram per day.

The average fat intake and specific study designs are shown in the bottom two rows. For each of the short-term studies, the fat intake was greater than or equal to 100 grams of fat per day. In the long-term study, the fat intake was not standardized.

Creon and Zenpep were crossover placebo-controlled studies. Pancreaze was a parallel placebo-controlled study which used a randomized withdrawal design. The liprotamase dose ranging study was a three-arm parallel study with three fixed doses. The liprotamase pivotal study was a parallel placebo-controlled study, and the liprotamase long-term study was an open label uncontrolled study.

We remind you that cross-study comparisons should be done with caution.

For your reference only, we have tabulated change in CFA in the registration trials of the

porcine-derived PEPs alongside those of liprotamase. In the left three columns, change in CFA results of the three approved PEPs -- Creon, Zenpep and Pancreaze -- are shown. In the right three columns, change in CFA results of the liprotamase dose ranging and pivotal studies are shown.

The most important results on the slide are the overall change in CFA and baseline CFA less than 40 shown in the first and second rows. The overall change in CFA results are shown in the first row.

Recognizing the limitations of cross-study comparisons, the porcine-derived PEPs appear to have numerically higher changes in CFA than liprotamase. The PEP saw changes in CFA of 26 percent with Zenpep, 33 percent with Pancreaze, and 41 percent with Creon.

It should be noted that Creon had a higher dose than the other two studies and exceeded the upper limit recommended in the CFF guidelines.

The liprotamase pivotal trial had a change

in CFA of 11 percent. It should be noted that in the dose ranging study, the increase in CFA was less than dose proportional. It should also be noted that the high dose of the dose ranging study also exceeded the upper limit recommended in the CFF guidelines.

Maximizing the dose in the liprotamase dose ranging study did not lead to a great increase in change in CFA in contrast to the Creon study, where maximizing the dose led to a substantial increase in change in CFA.

The change in CFA results in patients with baseline CFA less than 40 percent are shown in the second row. Once more, keeping in mind the limitations of cross-study comparisons, the porcine-derived PEPs appear to have numerically higher changes in CFA than liprotamase in this subgroup, as well. The PEP saw changes in CFA of 40 percent with Zenpep and 61 percent with Creon. The liprotamase pivotal trial had a change in CFA of 15 percent in this subgroup.

Looking at the results of the dose ranging

study, it should be noted that the change in CFA observed in the mid-dose arm was higher than that seen in the high dose arm. The change in CFA result in patients with baseline CFA greater than or equal to 40 percent are provided in the third row.

Now, on to safety. First, overall exposure. The total liprotamase safety database consists of almost 500 patients, 433 patients with EPI due to CF, 39 patients with EPI due to chronic pancreatitis or pancreatectomy, and 20 healthy individuals.

This slide shows the overall exposure by study, dose and duration. The dose ranging study was in 117 patients for four weeks with the three doses shown. The pivotal study was in 138 patients for five-and-a-half weeks with the dose shown. The long-term studies were in 163 patients for six months and 149 patients for one year.

It should be noted that 29 of the 39 patients in the long-term chronic pancreatitis study, which is Study 810, completed three months,

14 patients completed six months, and only four completed one year.

Now, on to the key safety issues. One of the rare but serious conditions seen most often with prolonged high PEP exposure is fibrosing colonopathy. The exact mechanism of this condition is still unknown. Because it is rare, fibrosing colonopathy has not been seen in the clinical trials of PEP and was not seen, nor would it be expected to be seen, in liprotamase clinical trials.

There is concern about a potentially greater risk of fibrosing colonopathy with liprotamase than with PEPs. This could be a possibility in some patients who, because of poor control of their EPI symptoms, had their doses increases excessively. In addition, there could be a theoretical risk related to the crystallized cross-linked lipase, which, being more resistant to proteolysis, could cause persistent lipase activity in the colon.

Another safety concern that previously existed for pediatric patients treated with

porcine-derived PEPs was the potential for growth retardation and malnutrition. Previously, since PEPs were not FDA approved drugs, variability existed in their efficacy. Thus, pediatric patients could potentially be treated with an ineffective PEP and subsequently have growth retardation and malnutrition.

Although there have been no direct comparisons of liprotamase and PEPs, in light of the magnitude of change in CFA observed, we are not sure liprotamase can support the optimal growth and nutrition of these patients and whether a clinical benefit will follow.

During the clinical development program, concern regarding elevated transaminase levels was initially raised with the Phase 2 dose ranging study. In this slide, the first row shows the number of patients with transaminase elevations greater than or equal to five times the upper limit of normal. The second row shows the magnitude of these elevations.

There appears to be a trend of greater

number of patients with elevations greater than five times the upper limit of normal with increasing dose. Also, there appears to be a trend of a higher magnitude of transaminase elevations with increasing dose.

There are no Hy's Law cases in this study or in any of the other liprotamase studies. Hy's Law was defined earlier, but I'll define it again. There were no cases of threefold or greater elevations above the upper limit of normal of ALT or AST accompanied by twofold or greater elevations of serum bilirubin.

The remainder of my discussion of transaminase elevations will focus on the pivotal and long-term studies because the product in the dose ranging study differs physicochemically from the product used in the pivotal and long-term studies.

Now, Study 726, once again, the pivotal study. We remind you that the pivotal study had an open label treatment period of three weeks before the randomized, double-blind treatment period of

one week. Thus, the patients in the liprotamase treatment group had only one more week of exposure than those in the placebo group.

There was a numerically higher number of patients with elevations greater than five times the upper limit of normal in the liprotamase group than the placebo group. The magnitude of the transaminase elevations appear to be higher in the liprotamase group compared to the placebo group.

Shown here are shift tables for ALT comparing baseline values, maximum values before start of treatment, and maximum values during treatment. The shift table for placebo is on the top, and the shift table for liprotamase is on the bottom.

In blue shading are patients that shifted into a lower elevation category than baseline. In gray shading are patients that stayed in the same category as baseline. In yellow shading are the patients that shifted into a higher elevation category than at baseline.

No difference was appreciated between the

two treatment groups, except that only the liprotamase group had two patients that shifted into the 5 to 10 times upper limit of normal category, shown here in red text.

Here is the corresponding table for AST. No difference was appreciated between the two treatment groups. Note that one patient in the liprotamase group and one patient in the placebo group shifted into the 5 to 10 times upper limit of normal category, shown, again, in red text. Because the exposure in the liprotamase group was only one more week than the placebo group, these results are difficult to interpret.

Now, on to the long-term study. This table shows the range of transaminase elevations by timeframe. The proportion of patients in the 2.5 to 5 times upper limit of normal and 5 to 10 times upper limit of normal categories was numerically higher on treatment compared to at baseline screening or last value.

Another issue identified in the liprotamase safety dataset was distal intestinal obstruction

syndrome, or DIOS. DIOS involves blockage of the intestine secondary to factors such as thickened intestinal contents and is known to occur in individuals with cystic fibrosis. This slide describes the cases in the short-term studies.

In the pivotal study, one patient was diagnosed with DIOS during the no treatment phase when the usual PEP was withdrawn. In the dose ranging study, three patients were diagnosed, one in the low dose group and two in the high dose group. The low dose group patient was diagnosed three days after start of liprotamase. The first high dose group patient was diagnosed the first day of liprotamase treatment. Symptoms started in the no treatment phase, but worsened during the study.

The second high dose group patient was initially diagnosed two days after stopping the usual PEP, but received three doses of liprotamase.

In summary, most of these cases occurred either when patients were taken off their usual PEP or shortly thereafter.

Now, the long-term study. Three patients

had DIOS. The first patient developed symptoms within one week after starting liprotamase, the second after about a month, and the third after about three months. Note that the first patient continued from the dose ranging study and had an episode of DIOS in that study, as well. Note, also, that there was no concurrent comparator arm.

Now, the risk-benefit considerations. We question whether the magnitude of change in CFA observed will be associated with a clinically meaningful benefit. In the overall study population, the change in CFA with liprotamase relative to placebo was 11 percent.

In the subgroup with baseline CFA less than 40 percent, the change in CFA with liprotamase relative to placebo was 15 percent. Because CFA is a surrogate, we question whether this level of change will translate into growth retardation in pediatric patients and if this level of change in CFA will translate into cases of DIOS.

DIOS was observed in the liprotamase dataset, but was not observed in the PEP clinical

studies datasets. This could be due to a larger liprotamase safety database. This could also be due to lower efficacy of liprotamase, leading to more malabsorption.

Now, the fibrosing colonopathy risk. This risk may increase with liprotamase if the dose is excessively increased in response to lower efficacy. There were no fibrosing colonopathy cases observed in the studies, but cases would not be expected given the rarity of fibrosing colonopathy and the size of this database.

In addition, there could be a theoretical risk related to the crystallized cross-linked lipase, which, being resistant to proteolysis, could cause persistent lipase activity in the colon.

We emphasize that this is a new molecular entity. There are no data available for long-term exposure beyond one year. Less than 150 patients were exposed for one year. This is in comparison to PEPs, which have multiple decades of clinical experience and are extensively described in the

medical literature.

An additional safety issue is the transaminase elevations greater than five times the upper limit of normal. There was no signal for such transaminase elevations with the PEPs, but there was a limited safety database with one short-term trial in approximately 30 patients for each PEP.

To summarize the risk-benefit considerations, the change in CFA for liprotamase was modest. There is limited data on the actual doses that will be used for maximum improvement of EPI-related steatorrhea. The dose ranging study showed the increase in CFA was less than dose proportional.

The long-term study lacks design features that would allow a robust, quantitative assessment of drug effect. Safety concerns include fibrosing colonopathy from upward dose titration, DIOS from decreased efficacy, and growth retardation in pediatric patients also from decreased efficacy.

This concludes the FDA presentations. Many

people worked hard on this challenging project and I'd like to acknowledge their contributions on this slide.

Clarifying Questions from the Committee to FDA

DR. RAUFMAN: Thank you. We'll now ask if the committee has questions for the FDA, and perhaps I'll start.

Dr. Dannis, in one of your initial slides, it's stated that a greater than or equal to 30 percent increase in CFA was determined to be clinically meaningful. I'd just like clarification of how that threshold was determined for one of these agents having a clinically meaningful effect.

DR. MULBERG: The standards that were used to define the greater than 30 percent were based upon the interpretation of historical literature data, as well as the only one published placebo-controlled data that did demonstrate, with a different product, the greater than 30 percent difference.

I think it's accepted that steatorrhea is a

significant clinical problem, is defined in different ways, and the contributors to understanding what severity really means had to be taken into context. And the data published in approved trials support some of that data.

DR. RAUFMAN: Because I would just comment on one of the comparative data slides had shown that one of the approved PEPs, Zenpep, did not achieve that threshold. I think the CFA for Zenpep was 26 percent; so just as a comment.

DR. DANNIS: I think that, in general, we looked at the totality of the data, and we spent time with the short-term trials looking at individual patient results. So that is correct. It's less than 30 percent. It's an average amount for the overall group.

We also looked at the patients with baseline CFAs less than 40 percent, which had a significant change of 47 percent. So although we did make the statement about 30 percent, I think that we spent enough time or a lot of time looking at all of the submissions and all of the data that was contained

in them on the individual patients to see how each individual patient actually did.

DR. RAUFMAN: Thank you. Dr. Hubbard?

DR. V. HUBBARD: I have a couple questions. One is on -- I guess it's to Dr. Zhou on the analysis of the stability of the enzymes in the different food solutions.

I'm assuming that you used standard pH enzyme methodology for doing the activity levels, but you didn't say how you actually assayed. What were the conditions? Was the enzyme activity in the food solution or was it under standard enzyme methodology, buffers and whatnot?

This is basically to your slides 25 and 26.

DR. ZHOU: Yes, because if I remember correctly, for at least two of the enzymes, the samples were taken out of the incubation, which has the food matrix in it, and they did some dilution and then assayed. They used the tributyrin for lipase and then modified USP for protease and amylase. So there is a food matrix present in those samples, if that answers your question.

DR. V. HUBBARD: But the enzyme was actually measured in a more standard, buffered milieu. It wasn't just assayed directly in the food solution. I'm just trying to figure out --

DR. BURCKART: You understand that these assays were not done by the FDA. These were done by the applicant, and that was part of the comment about validation. You're referring to validation.

DR. V. HUBBARD: Okay. And my other main question -- and it also does relate to the use of the 30 percent, but on slides -- in the presentation, on slides 38 and 40, you say the primary efficacy endpoint was done in subjects that had a baseline less than 40. Yet, the baseline CFA values in your slide 40 are above 40. So I just don't know how to interpret that discrepancy.

DR. DANNIS: That was a mean value.

DR. V. HUBBARD: Right. But it was said that the primary efficacy analysis was done in patients with baseline CFA less than 40.

DR. DANNIS: That's correct. So there were patients that had baseline CFAs less than 40 in the

trial, as well as other patients.

DR. V. HUBBARD: But when you say this baseline, slide 40 is all subjects then.

DR. FARR: That is for the whole population.

DR. DANNIS: Right. So in the trial --

DR. V. HUBBARD: It wasn't clear whether that was for the whole --

DR. DANNIS: Yes. That was for all the patients in the study.

DR. RAUFMAN: Dr. Lowe?

DR. LOWE: One question. Did you look at the BMI data to see if the drop from the beginning to the end was statistically significant? With those small numbers of patients and huge standard deviations, is that a real drop?

DR. RAJPAL: Are you talking about Study 767?

DR. LOWE: The slides, you mean? If you look at -- it looks like slides 51, 52, 53. The point was made that there was an initial drop in BMI and then that never returned to the original value.

My question is, is the original value and the endpoint value, are they statistically different?

DR. RAJPAL: I don't believe it was presented in the study report, but the sponsor might want to comment on that.

DR. RAUFMAN: I guess the sponsor can think about that for a minute.

Dr. Fogel, you have a question?

DR. FOGEL: I have a question about the underlying premise. It's my understanding that surrogate markers were meant to be markers that relate to the outcome of importance, which, in this case, would be the BMI.

Is there any data that shows that a 30 percent change in CFA relates to changes in BMI, whereas a change of less than 30 percent doesn't alter BMI? Because that's the underlying issue that we're dealing with, to me.

DR. DANNIS: I think it's difficult in this particular situation, because the approvals that were done for the porcine PEPs were done in a very

different way than other approvals, because of the information that I presented. We accepted the surrogate marker with a short-term study and felt that looking at the change in CFA was an appropriate way to see the efficacy of the individual trials. So we don't have information on long-term studies with BMI outcomes.

DR. MULBERG: If I may add, though, I think you do have the historical perspective of what's known since the initiation and adoption of pancreatic enzyme product therapy is part of a regimen for the treatment of CF patients that goes on for decades. And if you look at the CF registry data longitudinally, you see that, clearly, growth and nutrition and survival have improved. So it's maybe supportive aspects of that question.

DR. FOGEL: And I agree with that. I think that's very compelling data. The number 30 just seems arbitrary. Is there any data that less than 30 doesn't alter BMI, whereas more than 30 -- that 30 percent change is the minimum required to get the improvement in BMI that we're talking about?

DR. MULBERG: I don't think we're aware of any data.

DR. RAUFMAN: Dr. Krist?

DR. KRIST: I was just trying to understand Study 767. And, Dr. Dannis, I heard you mention that there was no protocol-specified efficacy endpoints, and you characterized it as a long-term safety study.

I heard the sponsor say that they prospectively defined that they were going to measure weight, height and BMI. I was just trying to understand the disconnect or the difference between the two.

DR. FARR: Our policy is that we usually look at studies that already have been designed and we have talked to the sponsor about it ahead of time. And we look at the well controlled and adequate studies, and this study was not well controlled.

It's good information, but it's not really proving anything at this point. So we cannot really scientifically say, yes, this is a good

pattern, because it wasn't based on scientific information to begin with.

DR. RAUFMAN: Could you please identify yourself?

DR. FARR: I'm sorry. Shahla Farr. I'm the statistical reviewer.

DR. DANNIS: Can I just make one more comment? Those phrases were taken directly from the study report.

DR. RAUFMAN: Dr. Joad?

DR. JOAD: I'm just curious, from the FDA, why you thought CFA was okay for this, as a surrogate for this new product, rather than BMI, height, weight, things that really matter? Why did you work with the company to say this was a good way to look at it?

[Pause.]

DR. RAJPAL: We're just discussing that for a minute and we'll be able to answer in a second.

DR. GRIEBEL: I'm Donna Griebel. I'm the division director. Unfortunately, all the sidebarring is we all predate the original group

that made the agreements for the development of the study. But I think we all agree that this has been the paradigm for development of this product line, PEP products, certainly what's in the literature.

It's very difficult to measure, from a clinical trial standpoint, the hard clinical outcome endpoints of growth and development, lung function, survival.

So we are making some suppositions based on the fact that we weren't the ones that made the agreement, but it did make sense to do it, because it was a surrogate that had been used and it has a longstanding presence in the literature.

Certainly, if we had seen -- I mean, the message that you're seeing in our briefing document and our presentations, what we're asking you is it appears that there's a lower delta in the CFA with this product and is that meaningful. If we had seen something that was comparable to what we've seen with the other products or within the literature, we probably would have been much more comfortable with this.

DR. RAUFMAN: Thank you. Dr. Hasler?

DR. HASLER: First, one comment, and then a few questions. My concern is that the FDA is comparing apples and oranges when they're comparing liprotamase to the porcine products. You're taking a well designed, rigorously adhered to protocol and comparing it to three relatively small trials, which I believe were used to reestablish use of the porcine products in the marketplace.

My first question is, what were the FDA's criteria to get these porcine products reapproved? Were they asked to achieve a 30 percent CFA?

I guess my second question relates to other data which may be out there that we haven't heard about. There's several thousand people followed in the cystic fibrosis database.

Do we have data on fecal fats or other things which might be used to support the FDA's contention that porcine products do seem to be more potent than liprotamase?

DR. RAJPAL: Your first question was about the 30 percent cutoff. That is for the baseline

CFA less than 40, where we were looking at that. And I didn't go back and look at the regulatory history of what we told each of the companies back then, but I think that was before I had started reviewing these products. But I believe that it was the same standard similar to what we told this company, that in the baseline CFA less than 40, you want to have 30 percent or more.

We did review the literature and there are articles in the literature showing that comparable to what we have here, that the results we see for Creon, Zenpep and Pancreaze are similar to other pancreatic enzymes. And there was a review article, I think, recently, from 2010, that reviewed a number of articles. One of them is Konstan, where they discuss the Ultrase product and they showed similar results.

I'm sorry. I forget the second question now.

DR. HASLER: That was the second question.

DR. RAJPAL: Okay.

DR. DANNIS: I just want to add that we know

there are limitations to comparing the PEPs to liprotamase, and the table was put up because it's difficult for us not to remember the knowledge that we have from all the other products.

They are pancreatic enzymes, and we do have all of the data from not just the approved studies, but all the other studies out there that are all similar. And when we looked at all of the information that we've gathered over the years, it was difficult not to keep the history and the information that we have and not to compare it to what we have now.

DR. RAUFMAN: Dr. Mulberg?

DR. MULBERG: Thank you. I have two additional comments just to extend my colleague's previous comments, Dr. Hasler. The burden of proof was the same for all the sponsors of the porcine-derived products.

The second point that you raise I think really is part of the burden that Dr. Raufman must share with the GI Advisory Committee about the value of this difference between liprotamase's

delta in CFA, its clinical relevance, and its potential impact upon patients with cystic fibrosis and other disease.

DR. RAUFMAN: Dr. Lightdale?

DR. LIGHTDALE: I have two questions. They're very different. So I'll ask one that's easier. The first is, in the process of doing the porcine studies, was there a standardization of the definition of DIOS? It actually can be a very subjective diagnosis. I'm just curious if out of that came a standard definition, if that's something you can use as an endpoint.

DR. DANNIS: So your question is whether there was a standard definition of DIOS. I don't recall that there was. However, in reviewing some of these products, one of -- intestinal obstruction is another way to describe DIOS, and I don't believe there are any cases of those in the approved PEPs to date.

DR. LIGHTDALE: Okay. And then the second question is, just thinking from the FDA standpoint, are you in the habit of approving drugs that may

not be as effective as other products that are out there, but are known to be effective or found to be effective?

DR. DANNIS: That is an excellent question and that is why we are here.

DR. LIGHTDALE: Have you done it? Is there precedence?

DR. RAJPAL: I'm not really sure about whether there's precedence. Somebody else might be able to answer that. But I really just wanted to point out that the reason we're concerned here is what we said in the slides, the fibrosing colonopathy if there's upward dose titration and the potential of that and, also, potential for growth retardation.

I also want to point out, on that slide 70, where we had the porcine-derived PEPs and the liprotamase -- that is slide 70. So in the dose ranging study, we were concerned that there wasn't a dose proportional increase. So if there is upward dose titration, there might be excessive upward dose titration. So that's what we're really

concerned bout.

Somebody else might be able to answer your other question.

DR. RAUFMAN: Dr. Beitz?

DR. BEITZ: I just wanted to make a couple of comments here. One is that although we and the sponsor have been talking about some of the other products that have been approved, what matters most to us today in this discussion is the benefits and risks of this product as it will be used in the target population. So that's really what we need to focus on the most.

We are checking to pull up a copy of a guidance to industry on the pancreatic enzyme products to see what, if any, specific guidance there was given formally regarding the CFA and the magnitude of change, and we'll get back to you either now or after the lunch break.

DR. RAUFMAN: Dr. Van Hubbard?

DR. V. HUBBARD: I have an additional question to really follow-up on Dr. Raufman's first question on this series, and that is relating to

the 30 percent CFA differential.

I have a question, and I'm not sure if the FDA has the information or whether the sponsors may have some additional information. But in terms of the range of CFA and the subjects off enzymes, in my experience, it's been atypical to have the CFA of even untreated people, less than 40 percent.

So to put out there a 30 percent improvement seems to be an odd number, in my interpretation. In the studies I've done, a lot of the CF patients have had CFAs basically in the realm of 60 percent in off enzymes. So to have a 30 percent improvement in the majority of the candidates for such therapy -- I can see a 30 percent relative improvement rather than a 30 percent absolute improvement.

I don't know whether there's any data on the prevalence or the distribution of CFAs in the targeted population. But otherwise, I still think a 30 percent improvement in relative CFA should be at least considered.

DR. RAJPAL: Well, must looking at the

table, for Creon, it was a 61 percent change in that subgroup. I'm sorry. Maybe I misunderstood your question.

DR. V. HUBBARD: I'm referring to the total targeted population. That 61 percent in that PEP data was all on subjects that had CFAs of less than 40 percent, which, again, in my experience, is the more atypical subject.

DR. MULBERG: I will answer it by saying that Dr. Durie presented at least one perspective of the -- a spectrum of coefficient of fecal fat from the Toronto experience. And I don't recall all of the dots, but the great majority of the slide point was that most patients do not really reach the greater than 80 percent cutoff of so-called normal coefficient of fat.

I would say, from a clinical perspective, there's a wide spectrum of steatorrhea when you quantitate it. The contributors to that are numerous, including, as you know, small bowel overgrowth, which is a completely different effect upon the measurement of fat in stool.

I can't quote all the historical literature data, but Dr. Rajpal did mention at least one study that was done, placebo-controlled, where the range of fecal fats were far below or as close to 40 and 50 with deltas of greater than 30.

DR. RAUFMAN: Did the sponsor want to comment?

DR. BRETTMAN: Yes. In response to Dr. Hasler's question, I'd like to ask Dr. Durie, because I think he can answer that question.

Dr. Durie? Dr. Borowitz?

DR. BOROWITZ: If your question is the data of CFA when patients are off enzymes -- is that a correct statement? If you can put up slide 058. This is our data, but if you look at all of the published studies, it's representative of the starting levels. This test runs from values in the teens to values up to 90 percent in patients with CF off of enzymes.

This data that we're showing you is our data for the placebo population in our 726 study. These subjects were studied about a month apart under

identical conditions. They ate identical food at approximately 100 grams of fat per day, and they don't always have identical CFAs.

So not only is there wide variation in the CF population, with an average that's around 50 percent because of the distribution, but, also, it's not a test that has very tight test/retest values.

Again, I want to emphasize the difference between a CFA off enzymes and a CFA on enzymes, which is the scatter plot that I showed you earlier.

I believe Dr. Durie has something else he'd like to add. Thank you.

DR. DURIE: What I'm going to describe are not study patients. These are patients that were studied in a clinical situation, where fecal fat balance studies were performed in over 240 patients.

Slide up, please. And these are data on patients that are on enzymes, not off enzymes, on enzymes. And the point that I'm trying to make is

that the percentage of patients on the vertical axis, and on the horizontal axis, we're representing CFA on the basis of fecal fat excretion. So less than 10 percent means 90 percent; CFA, 11 to 20 percent means 80 to 89 percent, et cetera.

As you can see, in a large population of clinical patients, about a third of the patients achieve a CFA of greater than 10 percent, about a third, around about 11 to 20 percent, and the remaining patients on enzymes show severe steatorrhea, continuing severe steatorrhea. These are all patients that are on PEPs.

DR. RAUFMAN: Thank you for that clarification. Before lunch, we have time for two more questioners. Dr. Shih?

DR. SHIH: This question is for the FDA, for the presentation in the comparison of Phase 2 and Phase 3, where you mentioned manufacturing development and you observed the changes occur in drug substance and drug product manufacture. And that was your slide number 19.

But the two bullets under the heading were all addressing product quality, not drug substance. So I want to hear more about the changes that you observed in the drug substance side; also, when you mentioned changes in product quality, whether that quality became worse or better. That's number 19 in your slides.

DR. LACANA: Yes. If you could put up the slide, please. What I referred to is product quality characteristics, which means we looked at particular attributes of the drug substance. In this case, I was referring to drug substance.

Unfortunately, I cannot go into details too much, because this is proprietary information.

DR. SHIH: Just did the quality become worsened or better?

DR. LACANA: It's different. There is no better or worse. It's different. And due to these differences, we cannot make an assessment on clinical performance.

DR. SHIH: Okay. How about drug substance?

DR. LACANA: That's our assessment. There

are no differences in the final drug product. So the difference that we noted when particular analytical assays were run on the Phase 1/2 material versus the Phase 3 material, the results of those assays indicated that the two products were different.

DR. SHIH: Okay. So I think I didn't get my answer, but let me ask a question that is related to this in the clinical side. And you may not be the right person to answer this, because I'm referring to the clinical study design.

Now, when you designed Phase 3 -- that's my guess, and the drug company probably, based on the Phase 2 result, to design their Phase 3 study -- so what was the basis that you will accept their design for looking for a delta and the power for that?

So what's the assumption and whether the assumption was met or not. In my reading, the company's design was that they're trying to detect -- I'm guessing, because I don't have the material of your protocol -- that you were looking

for delta equal to 11 percent based on your Phase 2 study, and then your power for that, which you have achieved in detecting the difference in your Phase 3 and based on your Phase 2 results.

So I'm asking FDA. When you discussed the Phase 3 study with the company, did you accept their design as detecting, with their product sample size, for a power of X percent power, so a delta of the CFA equal to 11 percent?

DR. LACANA: I will let Shahla answer that, but I wanted to make one clarification. When I said that the drug products were not different, I meant that the formulation, the final formulation was not different.

So the drug product itself was different due to the differences in the drug substances. I just wanted to make that clarification.

DR. FARR: Regarding us accepting what the sponsor has done, we apparently had several meetings with the sponsor, and perhaps the medical reviewer is the better person to answer this. But we specifically have asked the sponsor over and

over again that this is -- we would want to look at 30 percent or more in change from baseline, and, apparently, there was no positive response from the sponsor. But we have asked them. We've had meetings and we have asked them, that's what we are looking for.

DR. RAUFMAN: Last question. Dr. Hubbard?

DR. R. HUBBARD: Thank you.

DR. RAUFMAN: Hold one second for FDA.

DR. BEITZ: If I could just interject. We did pull up the guidance to industry that is on the website, and I'm just going to read you the section on endpoints, since it's relevant to some of the questions.

So what we've said here -- and, again, this is directed to manufacturers of the porcine pancreatic enzyme products. But what we're saying here is that although demonstrating a beneficial effect on clinical outcomes is desirable in clinical trials, and we give examples of weight gain or change in nutritional status, we also are accepting efficacy as being demonstrated by showing

a meaningful beneficial effect on appropriate pharmacodynamic measures, such as steatorrhea, and then we go into examples of the 72-hour stool collection that we've been talking about.

So, formally, the guidance officially in this particular instance doesn't give a particular cutoff. It leaves things somewhat open to interpretation with the language "meaningful beneficial effect."

So I think what we would like most to hear from you all today is whether a meaningful beneficial effect on CFA has been demonstrated in this NDA.

DR. RAUFMAN: Dr. Hubbard?

DR. R. HUBBARD: I guess I just wanted to make an observation and a comment. There seems to be a lot of discussion trying to compare the CFA results for the liprotamase early studies versus those for PEPs, and I just want to remind everyone that those are not head-to-head studies.

They had different protocol designs. They were done in very different time periods and

different sets of patients. They weren't crossovers. So we really should not over-interpret that data.

Then with regard to have drugs ever been approved that are inferior to other ones, oftentimes, you don't know because they're only done in placebo-controlled settings and only years later are the appropriate head-to-head studies done, which can meaningfully and clearly give you the robust data to say whether a drug is inferior or non-inferior or superior to another one.

So a lot of the times, we just don't have the data. And I think as a result of that, we do have to look at some of the robust clinical data that we have to support the CFA information the sponsor generated.

DR. RAUFMAN: Okay. We'll now take a 45-minute lunch break. We'll reconvene again in this room 45 minutes from now at 1:00 p.m.

Panel members, please remember that there should be no discussion of the issue at hand during lunch amongst yourselves or with any member of the

audience.

Thank you.

(Whereupon, at 12:16 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:00 p.m.)

Open Public Hearing

DR. RAUFMAN: We'll call the meeting to order. We'll now proceed with the open public hearing session.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your

attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Do we have participants? Dr. Campbell?

DR. CAMPBELL: Thank you. My name is

Preston Campbell and I'm the medical director of the U.S. Cystic Fibrosis Foundation in Bethesda, Maryland. I'd like to, first of all, thank the FDA and Kristine, in particular, for inviting me and CF patients and family members and giving us an opportunity to speak to you today.

With respect to personal conflicts, I have on financial relationships, personal conflicts. I've never been paid by predecessor companies representing liprotamase or Eli Lilly for any of those activities. And the Cystic Fibrosis Foundation has sold its rights to liprotamase to avoid any potential conflicts.

As to my background, I am a pediatric pulmonologist and have been involved in cystic fibrosis for 25 years now either as a CF center director or at the Cystic Fibrosis Foundation and regularly still see patients at Johns Hopkins.

My role at the CF Foundation is to oversee the clinical programs nationally, the basic science, and, relevant to today's discussion, the drug discovery and drug development programs, of

which there are over two dozen at this time. I've been in this role now for 12 and a half years.

Just a quick word about porcine pancreatic enzymes, because I think it's important that we make the point that we're extremely thankful for existing porcine pancreatic enzyme products. They have been life-sustaining for the 90 percent of CF patients who depend upon them. And with respect to the FDA, we're very grateful to the recent NDA that has resulted in those products being safer, more stable, and allowing a more precise dosing.

With these improvements, therefore, the committee may wonder why the CF Foundation believes that the liprotamase product is a very important addition to the therapeutic regimen of CF patients, and I'd like to bring up three. And then if you'll allow me, I'll say a brief word about safety and efficacy considerations that came up during the discussions earlier.

The first reason that we were involved, and the main reason, is that as a recombinant enzyme, liprotamase avoids the inherent risk of a biologic

product. Should anything -- and I repeat, anything -- and I don't know that we're smart enough to know what could happen to a biological product, but should anything compromise the supply of porcine pancreases required for the production of the current pancreatic enzyme products, the impact on the CF population would be absolutely devastating. All the progress that has occurred over the last several decades would be undone immediately. In essence, CF patients would suffer and starve.

We believe diversification within this life-sustaining product line is critical. The FDA always considers the risk of approving a new therapy. Given the concerns about biological products, which we believe are real, we ask that you also consider the risk of not approving liprotamase.

The second reason is reduced pill burden. The CF Foundation believes that liprotamase will be valuable to CF patients because they'll take fewer pills.

CF patients will spend hours a day on their medical regimen and consume fistfuls of pills. Being able to reduce their pills for pancreatic enzyme replacement to one, two or even three pills per meal from five, six or seven pills is clinically significant for them and meaningful and we think will represent an unmet medical need for a significant number of CF patients.

The third reason relates to the manufacturing process that enables liprotamase to be acid stable. As you know, porcine products are enterically coated to prevent destruction in the acid environment of the stomach.

The process of liprotamase enables it to be stable without enteric coating. This, we believe, will enable it to ultimately be developed in a formulation that can be delivered as a liquid, which will be a major step forward for infants, young children, and individuals who -- the 11 percent of CF patients who require nocturnal gastrostomy tube feedings to maintain their weight.

We do believe that this is a major step

forward -- will be a major step forward in, obviously, an unmet need.

So there's three reasons, in summary, the CF Foundation believes that liprotamase will be an important addition to the therapeutic regimen, because it reduces the risk, it reduces the pill burden, and the ultimate liquid formation will be very significant.

As a practicing physician, I look forward to the option of prescribing this medication, because it's very different and everyone reacts differently to medicines.

With respect, briefly, to safety and efficacy, we believe the safety data is clear. We can speculate about fibrosing colonopathy, but the DIOS liver function data that we have seen is part of the background noise of any cystic fibrosis study in the literature.

Efficacy, briefly, CFA, we believe, is a relatively awkward outcome measure. Retest is very imprecise, as has been pointed out. We don't know the correlation with ultimate clinical outcome.

And certainly, as Dr. Hubbard mentioned, we cannot compare the porcine products and their efficacy to the liprotamase efficacy values because of very different study designs, patient selection, and dosing.

Yes, the CFA in the liprotamase trials, as the FDA I think has appropriately said, may be modest, but we believe that the BMI is reassuring. And myself and others who understand CF well strongly urge you to approve this therapy because of all the theoretical and real risks that it will bring to CF patients and diversify the product line.

So that ends my comments. And I would like to turn it over now to Joan Brooks, who is a CF patient from Massachusetts, who's an advocate for patients for both access and for patient education, as well as a number of important things in the community.

Joan?

MS. BROOKS: Good afternoon. My name is Joan Finnegan Brooks and I have cystic fibrosis and

cystic fibrosis-related diabetes. My brother and sister both died from CF, and I am one of only 800 people over the age of 45 living with CF in the U.S. Living with CF, at age 50, I am grateful for every breath I get to take.

I am here today representing the CF community. We could have filled this room with people with CF who would have told you they needed another drug option for enzyme therapy. But because of the risk of cross-infecting each other with dangerous bacteria, people with CF are advised by their physicians and the CF Foundation to avoid contact with one another.

As an active CF Foundation and community leader, I began my involvement with liprotamase when the company reached out for help to learn about patients' lives and GI struggles. My contributions eventually changed from volunteer to professional consultant and I saw firsthand their commitment and dedication to make an impact on CF with liprotamase.

I realize that we're talking about GI issues

associated with CF, but I want to mention the burden of care for the fatal lung disease associated with CF. The lung treatments people with CF take to maintain lung function on a daily basis would make your head spin; up to eight inhaled aerosol treatments taking one-and-a-half to two hours, oral antibiotics, airway clearance therapy of at least 30 minutes, exercise, not to mention the significant pill burden associated with pancreatic enzymes. This results in a very heavy daily burden of care. It's even worse when we experience pulmonary exacerbations, which happen frequently in our community.

I've spoken with hundreds of families and people with CF over the years and although fear of losing lung function is universal, everyone's day-to-day experiences are defined by the constant struggle to gain weight, take handfuls of pills with food, and manage their digestive symptoms. This is especially true in our younger patients and families. As a child, I could never gain enough weight, struggled with constipation, diarrhea,

belly pain and gas, and was markedly undersized, even though I ate like an NFL offensive lineman.

With all this focus on CFA measurement, I feel compelled to make a comment. In all my years of being treated at the CF Foundation accredited care centers, I have never had a CFA test done. It doesn't have real-life clinical meaning. What does matter, however, is my weight and height in my growing years. That has direct relation to my pulmonary health and overall ability to fight chronic lung infections, and, subsequently, my longevity. And for most people with CF, trying to gain weight using available enzymes is an unimaginable challenge.

My friend, Bob Coughlin, parent of an 8-year-old boy with CF, describes his son's experiences to me, quote, "Enzymes don't always work and Bobby has explosive, uncontrollable bowel movements for no known reason without warning. Picture a third-grader who, on a somewhat regular basis, goes through this experience that is known to everyone in his class because of the violent

nature and the beyond horrendous smell," end quote.

This is his child's reality, even after trying all enzyme brands. There are many similar tales of woe I could tell. We need to have more choices for enzyme therapy, since everyone's malabsorption is not solved with existing drugs.

I hate taking handfuls of pills with my food. It's embarrassing and invites unwanted attention. This is a quality of life issue. Kids especially don't want to appear different than everyone else and go to great lengths to hide or disguise taking enzymes or they skip them all together, with grave consequences. And many kids miss part of lunch or recess to go to the nurse to get their enzymes, which adds to the stigma they feel.

Having a therapy requiring only one or two capsules would offer tremendous benefit to the CF community. It would also simplify a complicated dosing regimen.

In my mind, I have a translation table of sorts about how many enzymes to take for different

meals. The range can double my average dose to eight capsules with a fatty meal, and if I get it wrong, I have abdominal pain and bathroom needs that require me to change my work schedule and stay home.

Even after a lifetime of experience, it is very difficult to titrate enzymes to mimic normal digestion. I've been taking porcine enzymes, coated and non-coated versions, for more than 50 years. Many in our community do not realize where enzymes come from and are disturbed when they learn about the pig source.

There is no alternative. If I allow myself, I shudder to think about the contaminants in ground-up pig pancreas capsules I have consumed in great quantities daily or the pounds of plastic I've ingested disguised as enteric coating.

I'll end with a statement from Bob Coughlin, the father I quoted earlier. "Please help my son live the precious days he has on earth in a way that is not embarrassing or painful, both physically and emotionally, and as normal and

healthy as possible."

Our CF community needs a different kind of enzyme to help people and families cope with this terrible disease. Please approve liprotamase. Thank you.

MR. MARSHALL: Hello. My name is Patrick Marshall, and I am joined by my wife, Martha, and our son, Chase. We are the parents and brother of an 11-year-old girl named Kate.

On February 18th, 2000, after an exhaustive seven months of doctor appointments, hospital stays, tests, physical pain, insatiable hunger, and sadness, a simple sweat test told us of Kate's genetic reality, the telltale sign of Kate's condition related to how far she had fallen off the weight curve, despite having presented many other traditional CF symptoms.

If Kate could have spoken, she would have told us how much her belly hurt and how she could never get enough to eat no matter how much nourishment we provided to her.

Within 48 hours of Kate's diagnosis, she

developed pseudotumor cerebri, which is the swelling of the brain linked, in our case, to severe malnourishment and vitamin deficiency. Her pain was so overpowering that she vomited several times and cried in agony, falling asleep only from exhaustion.

Kate was immediately admitted into Maine Medical for urgent care. To reduce the swelling, she received two spinal taps and was put on an aggressive schedule of prednisone, in concert with massive amounts of IV vitamins E, D, A and K. We nearly lost our precious baby girl.

We remained at Maine Medical for two weeks. Amongst the plethora of information associated with the CF diagnosis, we learned of a recent study linking the importance of weight gain in children less than 2 years old and long-term lung function. We also learned that she would be required to swallow plastic-coated porcine enzymes with every meal the rest of her life, a task which proved incredibly complicated, since she was still too young to swallow capsules. Thus, it was necessary

to sprinkle the enzyme beads on a spoon coated with applesauce before placing them in her mouth.

While we were grateful to know that she would be able to gain weight, we encountered dosing challenges and problems such as thrush, a painful yeast infection occurring in the mouth and tongue from the enzyme beads. A liquid-based pancreatic enzyme would have alleviated these issues completely.

Today, Kate is 11 years old, beautiful, intelligent, responsible, loving, and athletic. Thankfully, she is remarkably healthy, though we know the deadly position she would find herself in should the pigs where her enzymes derive ever suffer from a global pandemic or from problems associated with potential unknown contaminants found in the ground-up pig pancreas.

As parents, we constantly worry about what Kate would do without the 20-plus enzymes she takes daily. Severe GI pain would start immediately, followed quickly by dehydration, drastic weight loss, and more, ultimately resulting in death.

While fear surrounding her ultimate health can be consuming, it's imperative to remember that she's 11 and she, like all girls her age, does not want to stand out in the cafeteria, which is often what happens with so many enzymes to take. She simply can't be discrete.

For Kate, the approval of liprotamase likely means taking only one enzyme capsule per meal, granting her a small reprieve from her extensive daily regimen of oral and pulmonary medications, while aiding her compliancy, safety, quality and normalcy of life, ultimately leading her towards improved overall health.

In conclusion, please turn your attention to my wife, Martha, who has in front of her three glass containers. Container A represents the 500 plastic-coated porcine-based pancreatic enzymes Kate swallows per month. I counted them.

Could you imagine being 11 and having to swallow all these capsules on top of the 200 other oral medications she takes? That's a lot of plastic.

Container B represents the 165 liprotamase capsules, the approximate number Kate would have the benefit of taking per month if approved by the FDA, reducing her monthly intake by 335 capsules. That's 4,020 less per year.

Container C is empty. Sadly, it represents the months worth of porcine-based enzymes Kate would not receive in the advent of problems in the world's pig population, which, as you know by now, would have rapid and mortal consequences for our daughter and sister, not to mention the thousands of other CF patients in the United States and the rest of the world.

Please approve liprotamase.

MS. HEALEY: My name is Francine Healey. I'm a parent of three children, two of whom have cystic fibrosis; Amanda, who is 16, and was diagnosed in vitro; and, Mike, who is 19, and was diagnosed at three months when he was failing to thrive.

The immediate concern for Mike, as it is for every baby diagnosed with CF, was to gain weight.

At the time, he was prescribed one-quarter of a capsule of pancreatic enzymes with each feeding, and I vividly recall starting every day preparing the day's doses, opening up capsules and literally counting out the beads, separating capsules into four equal doses.

Pretty quickly, it became obvious that his pancreatic insufficiency was high and soon we were breaking open several capsules with each meal, shoveling them into our hungry baby's mouth with gallons of applesauce, which I carried with us always.

Both the medicine and the method of delivery left much to be desired. Being able to give a baby who has not yet developed the ability to swallow solids, a liquid formulation would have made life so much easier.

When Mike was a toddler, there were no suggested dosing limits for enzymes. The threat of a fibrosing colonopathy had not yet been determined. A well meaning fellow decided that we should try to get his bowel movements down further

and he began taking Ultrase MT25, a product since abandoned because of the damage it caused.

You can guess the rest. And though Mike stopped short of the fibrosing colonopathy disaster, he now deals with permanent colitis. Under his GI doc's direction, Mike is very careful not to overdose while still trying to put on weight.

Calculating or, rather, guessing the fat content of food and taking the appropriate number of capsules is a daily adventure. Mike is now a freshman in college. He is five-foot-seven and 130-pounds fully clothed. Mike's weight hovers on the 10th percentile, in spite of our very best efforts to get him closer to the desired 50th percentile, which has been demonstrated to correlate with significantly improved lung heath and life expectancy.

He takes five enzymes with meals and three with snacks, being careful not to overdose. This translates into approximately 25 pills per day, 750 pills per month, and since we must get three

months' supply at a time, that's 2,250 enzyme capsules with every shipment.

Our daughter Amanda's GI history is much less dramatic. Even so, she takes 10 to 15 pancreatic enzyme capsules a day, which adds another 1,000 pills to our quarterly enzyme shipment. We are drowning in enzymes.

Even though nutrition is enormously important in determining good health in CF patients, it is not the most onerous health responsibility they face.

Mike went off to college this fall with lots of medical equipment and bags of medicine. The reality of the enormous burden of care that living a life with CF entails hit him big-time. In addition to the normal adjustments of a college freshman taking personal responsibility, he is also managing a complicated health regimen solo.

When Mike was born, the average life expectancy for a child with CF was 21. Today, that statistic is in the late 30s. Even so, in the last four years, I have personally known five families

who have lost children to CF ranging in ages from 14 to 21. Statistics are not always what they seem.

It is a herculean effort to keep this population healthy, and anything that lightens the load makes the quality of a life lived with the burden of this disease better. A kid with CF carries his pancreas around with him in his pocket all day every day. They stuff fistfuls of pills down their throats every time they eat, and they need to eat a lot. It would make a huge difference in their lives to have an easier, less obtrusive, and more effective enzyme formulation.

You know, it's just these last few weeks that I've learned really for the first time that the current products we have are made from ground-up pig pancreases and coated in plastic. I have to tell you that I think 99 percent of the CF community is not aware of this either, mostly because we have no choice but to take this one product or fail to thrive. It's life or death.

If I spend much time thinking about the

amount of pig parts and plastics I have shoveled into my children, I could weep. We need alternatives. Please approve liprotamase.

MS. BROOKS: I'm back up here again speaking on behalf of -- I'm actually reading a statement prepared by Jane Holt of the National Pancreas Foundation. She is from Boston and was unable to make it down here because her flight got canceled.

"I would like to thank the committee for allowing me to speak today. My name is Jane Holt and I am cofounder of the National Pancreas Foundation. The National Pancreas Foundation provides education and support for patients with all diseases of the pancreas and for physicians and researchers that help these patients.

I am also a patient with chronic pancreatitis. The life of the patient with chronic pancreatitis is very difficult. Most of us struggle with constant pain and nausea. Some of us have constant diarrhea. For many of us, it is almost impossible to continue to work and/or care for our families.

There are very few things a doctor can do for those of us with chronic pancreatitis. Mostly, our doctors treat our symptoms. Enzymes, such as liprotamase, are one of these treatments.

There are several reasons why this particular enzyme is important for patients with chronic pancreatitis. Adherence to therapy is a problem for our patients. The enzymes that are available right now require the patient to take several pills with meals and snacks. Liprotamase only requires the patient to take one pill. This will be easier for the patient and most likely we'll end up with more patient compliance.

Even as a well informed patient and patient advocate, I know I personally struggle with compliance. Taking multiple pills every time I eat has definitely been an issue. So I know that this factor alone will be so helpful to our patients.

Liprotamase is not enteric coated. Currently, all of the approved enzymes are enteric coated. This enzyme begins dissolving in the stomach and duodenum, allowing for earlier

digestion of food. Some patients have found that their pain is decreased by non-enteric coated enzymes, but there are none available. This is a very important consideration for patients with chronic pancreatitis.

Again, speaking personally, I found uncoated enzymes worked better for me and provided me with some pain relief.

Liprotamase can be used as a powder. It can be mixed with water or applesauce for patients who have difficulty swallowing pills and for pediatric patients. It can also be used in feedings for G-tubes and J-tubes.

Researchers are beginning to understand a little bit more about pancreatic disease. Like liver disease, they expect that there will be several different diseases of the pancreas. As our researchers move forward, it is very important that they have a variety of enzymes to treat different symptoms of this disease.

The initial testing that was done for this enzyme on patients with chronic pancreatitis showed

improvement in many of the symptoms of chronic pancreatitis. I have heard from some of the doctors involved in that testing that the patients were upset they were not able to continue taking the enzyme after the study.

It is important to our patients that we have enzymes such as liprotamase available to help treat all the symptoms of chronic pancreatitis.

As a patient advocate and as a representative of the National Pancreas Foundation, I think it is important that our patients have options and choices and that together with their physicians, they can make informed decisions about how to best help manage the symptoms of chronic pancreatitis.

Chronic pancreatitis is not a simple disease and treating is not a simple procedure. There is no one-size-fits-all option for our patients. We need choices.

Approving this enzyme will give our patients another option, another choice in their ongoing battle with this disease. Thank you."

DR. RAUFMAN: Thank you. I believe there's one more speaker.

DR. CAROME: Good afternoon and thank you for the opportunity to speak to the committee today. I am Mike Carome and I'm testifying today on behalf of myself and Dr. Sid Wolfe from Public Citizen Health Research Group. And I'll note that we have no conflicts of interest.

I joined Public Citizen this month after serving for many years in the Office for Human Research Protections, HRP, and including the last eight years when I was the associate director of that office.

I'd like to begin by reiterating some of the things that were presented based upon FDA's review and looking at the risk-benefit analysis. And so starting first with the benefits of liprotamase, the FDA medical reviewer noted that in multiple pre-submission meetings, the division has stated that in a subgroup of patients with baseline CFA less than 40 percent, a greater than or equal to 30 percent difference between the liprotamase and

placebo groups would be considered clinically meaningful.

This data, which you've already seen today, summarizes the most important data presented from the one randomized clinical trial, Study 726, and highlighting the key information which presents the data in the subgroup that had CFAs less than 40 percent, which was the focus of the primary efficacy analysis. While the difference was statistically significant, it fell far short of FDA's pre-specified 30 percent difference for clinical significance.

This is an extraction of other data from another table which you have seen earlier today, which puts that study in the context of other studies for the porcine approved PEPs. And in all cases, looking at the overall data and in the most important baseline group with CFAs less than 40 percent, the CFA results for liprotamase were far lower than those for the studies on the PEPs, which led to their approval.

In commenting on the benefits in the

analysis of these data, the FDA medical reviewer noted that Study 726 demonstrated efficacy of liprotamase by achieving a statistically significant increase in CFA compared to the placebo group. However, the differences observed in this trial do not appear as large in magnitude as have been observed in studies of porcine-derived PEPs.

We note that there are limitations of cross-study comparisons. However, although the more severely affected patients had numerically larger increases in CFA with liprotamase, 15 percent, than less severely affected patients, the changes in this subgroup were not numerically as large as observed with the porcine-derived PEPs, 47 percent and 61 percent from the two PEPs that are derived from porcine.

Going on, the FDA medical reviewer explains why there may be a biological basis for the advantages of the porcine-derived products. While the porcine-derived PEPs contain multiple enzyme classes, including lipases, amylases and proteases, each of which may contain multiple enzymes with the

same catalytic activity, liprotamase only contains one enzyme for each class.

The complex nature of pancreatic enzymes is due to the fact that the crude extracts represent the typical enzyme output provided by the pancreas. As such, multiple enzymes in each major class function together in digestion of the components present in food. Therefore, it is biologically plausible that porcine-derived PEPs might allow for more efficient digestion of food in the intestines.

Turning now to the risk side of the risk-benefit equation. The sponsor asserts that on unexpected safety signals were identified. However, based on its analysis of the data, the FDA medical officer identified the following safety concerns: potential for inadequate growth and malnutrition in children; hepatic transaminase elevations; distal intestinal obstruction syndrome, or DIOS; and, the risk of fibrosing colonopathy.

With respect to inadequate growth and malnutrition, the FDA medical officer noted that this observation, smaller CFA difference, is a true

reflection of a smaller therapeutic effect on CFA associated with liprotamase relative to the approved porcine-derived products; administration of this product to children could result in impaired growth relative to treatment with porcine-derived PEPs.

For young children, where adequate nutrition is a necessity for continued growth, less efficacy is a safety concern since it could result in growth retardation and failure to gain appropriate weight.

With respect to the transaminase elevations, I think the data was clear today. The studies looking at liprotamase tend to show a consistent trend towards higher transaminase elevations, which were not seen in the FDA-approved products.

With respect to DIOS, the FDA medical officer summarized seven DIOS events occurred in six patients during the liprotamase clinical trials. In one patient, two events occurred more than two years apart.

It should be noted that no DIOS cases were observed in the clinical trials of the approved

porcine-derived PEPs. There is the concern that the DIOS cases occurred with liprotamase because of lower efficacy than the PEPs.

With respect to the fibrosing colonopathy, the FDA review executive summary noted fibrosing colonopathy, a rare but serious condition that may result in colonic stricture, has been associated with prolonged high dose PEP administration. The risk of FC with liprotamase could be higher than with PEPs if the dose is excessively increased in response to lower efficacy. PEP products are routinely titrated to optimize treatment effect.

In addition, theoretically, liprotamase might be associated with a higher potential risk of FC because its chemical features may render it more resistant to proteolytic activity, causing it to be persistently active in the colon.

I'd like to speak to some of the concerns that are raised in the sponsor's submission regarding some of the concerns and why liprotamase may be more advantageous. One is that the supply could be interrupted due to disease or other stress

to pig herds that are the sole source of these enzymes.

In response, we are not aware of any interruptions in the supply of any porcine-derived products previously. Such problems, although theoretically possible, are highly unlikely and do not justify marketing of the drug for routine use in the absence of such supply problems. Furthermore, supplies of liprotamase could be disrupted, as well, for different reasons, as has occurred with many other drugs in the past.

The concern regarding possible zoonotic viral infections transmitted from pigs to humans has been raised as a concern. This is a theoretical risk, but the FDA-approved labels for all three porcine-derived PEPs state, however, no cases of transmission of an infectious illness associated with the use of porcine pancreatic extracts have been reported. Furthermore, eliminating this extremely unlikely risk by using a less effective product with greater safety risk would not be a rational approach.

In terms of the daily pill burden, I recognize that that is an issue. Given the data demonstrating that liprotamase may be less effective than the porcine-derived PEPs, consuming a smaller number of less effective capsules would not represent an improvement in care of patients with pancreatic insufficiency.

I'm going to skip that for time. I'd like now to turn, based upon the analysis of all the data available, to just make some comments about the ethics of doing clinical trials in this arena.

It's our view, based upon the available data regarding the FDA-approved porcine-derived products and liprotamase, that there is substantial evidence that liprotamase is less efficacious than the porcine-derived PEPs and appears to expose subjects to greater risk.

We believe that a randomized trial comparing liprotamase to an FDA-approved active comparator today would not be ethical because equipoise would not exist. We believe that properly informed parents aware of the above information in the

context of the existing products would likely not consent to enroll their children such a study that doesn't expose them to something that provides additional benefits and it may expose them to greater risks.

We also note, furthermore, that given the data presented, such randomized trials would not satisfy the criteria for approval under FDA regulations concerning the additional safeguards for children in clinical investigations.

Finally, I'd like to address several of the questions that have been posed to the committee and give you what our answers would be.

So for question 1-A, in the overall Study 726 population, is the observed difference in change in CFA between the liprotamase group, 11 percent, and the placebo group, .2 percent, of sufficient magnitude to be clinically meaningful? Our response would be no, especially because of the greater benefit with FDA-approved porcine-derived products.

Question 1-B, in the subgroup of patients

with a baseline CFA less than 40 percent in Study 726, is the observed difference in change in CFA between the liprotamase group, 20 percent, and the placebo group, 5 percent, of sufficient magnitude to be clinically meaningful? Our response would be, in the context of the data presented on the FDA-approved porcine products and FDA's pre-specified 30 percent CFA difference, we would say clearly not.

Jumping to question 4, are there additional efficacy studies that should be obtained prior to approving liprotamase for EPI? We would say no, and as we discussed, we believe further studies would be unethical.

For question 5-A, are there safety concerns associated with the use of liprotamase in EPI that preclude approval? We believe the answer is yes, there are significant safety concerns raised by the data presented regarding inadequate growth and malnutrition, hepatic toxicity, and DIOS.

Finally, we would say no to question 6-A. Based upon the data available, we do not believe

that the benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI.

Thank you for your attention.

DR. RAUFMAN: Thank you. That concludes the open public hearing portion of this meeting. We ended that a few minutes early, and I've been asked by both FDA and the sponsor if they could address some of the questions from this morning for a few minutes. We'll start with FDA.

DR. BEITZ: Thank you. I just wanted to formally respond to Dr. Shih's question regarding the agency's view of the Phase 3 trial design. And so we were able to locate the minutes of a meeting that was held with the company in 2005, where we were asked whether we agreed with an improvement of at least 10 percent in mean CFA between treated and placebo groups, and whether that was a clinically -- whether we agreed that such an improvement would be clinically meaningfully.

Our answer was that we did not agree with that proposal, and then we go on to iterate what is actually on FDA slide 7, which was that an increase

of 10 percent or greater in mean CFA between treated and placebo group is not sufficient to provide a clinically meaningful improvement in fat malabsorption in patients with elevated baseline fat malabsorption.

Then we go on to also talk about the 30 percent, which is also on that slide; that in citing literature at this point in time, it being 2005, an increase of about 30 percent or more in mean CFA in CF subjects with severe fat malabsorption treated with conventional enzyme replacement therapy compared to placebo has been deemed to be an effective treatment.

DR. RAUFMAN: Dr. Mulberg?

DR. MULBERG: Thank you. I first wanted to start by thanking Dr. Campbell and the personal anecdotes from the public. They were very poignant and I very much appreciated them.

I wanted just to redirect some of the morning discussion for clarity for the advisory committee, especially with regards to the 30 percent focus.

Again, FDA has accepted this CFA as a surrogate marker built upon historical and other data published and submitted. And it's very important for this committee to understand and consider whether the 10 percent difference that is the focus of liprotamase's major effect is considered a minimally clinically important difference.

So I think it's just important for that to be stated outright for clarity moving into the questions for this afternoon.

Thank you.

DR. RAUFMAN: Thank you.

Any additional comments from FDA? And the sponsor?

DR. BRETTMAN: Thank you. I would just like to provide some clarification on some issues that were raised this morning, and I'm going to ask Dr. Borowitz and Dr. Durie to help me do that.

The first point is, in the design of the 767 long-term trial, it was not designed as an efficacy trial. However, the nutritional parameters, BMI,

weight, height, were predefined in the protocol in order to assess the ability of liprotamase to maintain nutritional status. A comment was also made that a comparative trial, long-term trial, could have been done, and I would like Dr. Borowitz to address that.

DR. BOROWITZ: Thank you. At the time that we designed the 767 trial, it was not possible to have an active comparator and, therefore, it's an open label trial. At the time, there were no FDA-approved products. As you know, porcine products have been on the market for a long time, and much of what we do is based on this sort of historical stuff.

I do think, as a CF provider, the FDA's requirement for improved safety in manufacturing has been important for porcine products, but those newly approved products were not on the market.

In addition, the previous products had a wide range of fill, as you're well aware. There would have been absolutely no way to truly compare doses.

Of course, it's not possible to do a placebo-controlled trial, absolutely unethical, when you're looking at these most clinically meaningful endpoints. And I think this gets us back to what we've all been grappling with this morning, a lot of thoughtful people around this table and in the audience, is a 30 percent number clinically meaningful?

That number, I will tell you, has been put out there without any evidence to support it. So as we began the 767 trial, which we began as a safety study, we were grappling with this, as well. Remember, we're advancing the science here.

Enzymes have been on the market forever. We kind of do things the way we do them because that's the way we've done them, and this is the first data-driven program to try to really find out what the right dose would be. But we've grappled with this issue, also. What is clinically meaningful? How would we know the answer to that? And the only answer is to look at the most clinically meaningful thing, which is growth, and that can only be done

over the long term. And the older the patients are, the longer you have to look to be able to see some real change.

So we designed 767 as a safety trial, but we did prospectively say that we were going to look at height and weight and BMI as safety measures. And then we said, well, maybe there is some way to put some context to that, not to -- it's clearly a weak study design, but, again, we're trying to advance the science here. So let's put some context to that.

I think we have a slide that shows what our matching criteria were for the registry study. Do you have that there? So when we kind of came to this conclusion that we needed some context for what was clinical meaningful, we -- if you could bring up this slide -- we took our entry criteria for the 767 study, and we took all of these things and found points in the registry that would allow us to match for those.

So we've not used -- again, there was a presentation about how to really design this study.

It would have been great if we had, but we did, in fact, try to match patients as closely as possible.

We needed to use CFA. CFA is a surrogate marker that can be used in short-term studies to look at dose ranging, to look at efficacy, yes or no, statistically significant, yes or no. But we need to back away from the idea that we really know what's clinically significant. I appreciate Ms. Finnegan Brooks' statement that as a patient, in her 50 years of life, no one has ever used CFA as a tool.

Last, I will say that in the real world, in response to the last speaker, porcine enzymes are out there. They have been used over a long period of time in 90 percent of patients and patients with CF get DIOS.

Is that because of the porcine enzymes? Is that because of CF? Patients with CF have transaminase elevations. Is that because of the porcine enzymes? Is that because of the background of CF? I think that we need to think about the fact that we are trying to advance the science in a

data-driven way and I believe that's what Study 767 does.

There are some issues that I believe Dr. Brettman also wanted to address.

DR. BRETTMAN: Yes. Just as a follow-up. So Dr. Borowitz did not address the feasibility of actually doing a long-term trial, and I'd like to ask her to come back and do that, because I think it's very important, because you can only do the best that can be done. So I just want to ask her to address that.

DR. BOROWITZ: Yes. So one could ask, okay, well, when we designed the study, okay, there was no FDA-approved product. We couldn't use a placebo control. There was just no regulation to how much dose was in porcine products. But now there are products that are available that are FDA-approved that have a narrower fill ratio, so couldn't we do that study now. I will say that I think an active comparator trial would not be accepted in the CF community. You heard from Dr. Campbell there are over two dozen products in the pipeline for

patients with CF.

Pancreatic enzyme replacement therapy is life-sustaining, but a comparator trial, an equivalency trial would require -- I don't know -- 500 subjects per arm, something like that, over the course of the year. That, to me, would not be ethical. It would remove subjects who are willing to participate in trials.

Now, remember, this is not easy. Patients are out there in the real world leading their lives. When they say they're willing to be participants in a trial, it's a precious resource.

So to design that type of trial I think would not be accepted by the CF community at this point in time.

DR. BRETTMAN: I'd just like to come back and make one other point about the registry and the weight loss that we've talked about earlier today.

I showed you in my presentation that the dip in the BMI Z scores was driven primarily by 23 subjects who lost 5 percent of their weight in the first three months. Nineteen of those 23 were from

non-U.S. countries, and I think you will remember how nutritionally compromised those subjects were. The CF registry, yes, it was done as a post hoc analysis, but it does provide valuable context for the consideration of the 767 results.

To try to put in context the fact that, yes, there was weight loss, and as you heard from Dr. Borowitz, patients lose weight with this condition, particularly in the most at risk age group between 7 and 12. So the CF registry does help us to try to put that into context.

If I could have the slide on, please. This is a BMI shift analysis showing subjects from the 767 study who had a shift to better or worse of .25 in a BMI Z score. This is primarily driven by weight during a study of this duration. And you can also see the same information presented there for the registry.

I think what you can appreciate when you look at the right-hand panels, where the BMI Z score worsened by greater than .25 over the course of the observation period, there is no real

difference between the registry. So I think this is important data for the committee to consider.

The last point I wanted to make -- and I wanted to ask Dr. Durie, one of the keys here is that liprotamase data has been repeatedly compared to the small porcine trials, as if that sets the threshold. And Dr. Durie's center has more experience doing these assays than any other center in the world, and I would like to ask him to offer his perspective.

DR. DURIE: Thank you, Dr. Brettman. I guess that I'm trying to make a very simple point, and the very simple point is that based upon our experience, achieving greater than 80 percent or 90 percent as coefficient of fat absorption in a real clinical population of patients is really not fair. In our experience, this does not occur in a real population. And so I'm actually quite amazed by how many of the patients in the porcine trials achieved that objective.

So I guess what I'm really trying to say is I don't think that's a real world look at the

results of porcine enzyme therapy in a CF population.

DR. BRETTMAN: Thank you.

DR. RAUFMAN: Thank you. I think there are a couple of comments from FDA.

DR. BEITZ: Just a clarifying point that we do accept active control studies where the active comparator is not approved, but in those instances, we also expect that the study drug beat the unapproved active.

DR. MALONEY: I'm Elizabeth Maloney, epidemiologist from the Office of Surveillance and Epidemiology. And I just wanted to say a few more additional comments about the comparison between the Study 767 and the CFF registry.

While we can see that the CFF registry offers the potential to explore longitudinal data, albeit retrospectively collected, there were differences in the way that the patients were treated in the two different studies, which need to be mentioned.

For instance, in the 767 study, patients

were required to keep 72-hour diet diaries for a substantial amount of the study duration, and the CFF registry report did not mention anything like that.

The 767 study also provided vitamins to the study participants for at least six months, and there was no mention whether or not that was provided in the CFF registry.

Also, the fact that only three clinic visits were required to be included in the CFF arm of this comparison, it would be interesting to know actually what is the comparison of the average number of clinic visits that were achieved in the 767 study compared to the CFF registry.

We think that these are important differences and, unfortunately, there was no statistical analysis that adjusted for these differences. That would have also been interesting.

Thank you.

DR. RAUFMAN: Thank you. We will now begin the panel discussion portion of the meeting.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the panel.

There are discussion questions and voting questions.

Before we bring up the voting questions, let's have one short round of additional questions to both sponsor and FDA. Dr. Shih?

DR. SHIH: I heard that one thing is the dispute between FDA and the company about the subgroup consistency. We are facing the same dataset, but, however, the company says they are consistent and FDA is saying that they are not.

So I'd like to hear one more round of your dispute of why you think it's consistent and why you think it's not consistent.

In light of this whether 30 percent or 15 percent, 11 percent change of the CFA is a cutoff for clinically meaningful change or not, I would like to ask whether, in your long-term study, the company, 767-810, while you measure the BMI Z score for long-term, have you measured the CFA

change in short-term? And if you do, I didn't see the presentation. But if you don't, why not, because you are trying to establish the clinically significant difference in the CFA?

It would be more reasonable for you to establish, based on the previous PEP data, in the observational way, just like we did it for LDL and CHD disease. We don't know whether a surrogate marker for a clinical disease is significantly changed or not, and you can do such a -- you don't have to do additional study, but you can do those historical data to do a correlation between the two.

So the first thing is about the subgroup, the dispute about the consistency/inconsistency. The second thing is whether your long-term study has measured CFA short-term or not and why not or if you do, then present the data, and let's look at the correlation between the two, your long-term studies.

DR. BRETTMAN: So the first part of your question, I believe, was about the dispute about

whether or not results were consistent. And so if I could have the slide on, please.

I made this point during my presentation, but I want to emphasize it because I believe it's very important. CFA is going to be tied to the patient population and the study design. I think Dr. Durie has made that point and we've made that point. I understand there's disagreement on it.

But if you look at the baseline demographics for the subjects enrolled in 726, you can see that there is a very nutritionally compromised group of patients; and, if you look at different country groups, the BMI baseline Z scores are quite different.

So these are different subgroups, and so some variability in subgroup analysis is, in fact, going to be related to that.

Now, if I could go to the last portion of my presentation, and please bring up the 726 and TC-2A results. Thank you. Slide on, please.

So our view that the results are actually quite consistent rests on --

DR. SHIH: No, no, no. You've misinterpreted my question.

DR. BRETTMAN: I'm sorry.

DR. SHIH: My question is about your 726, the subgroup analysis, the consistency around your subgroups. That's in your slide 57.

DR. BRETTMAN: Okay. Fair enough. The point I was going to make is that consistency in subgroups, consistency across studies, there's -- so the picture of consistency is not only in the subgroups; it's across studies, and there was statistical significance across different groups.

If you could please put on the slide 57. So this is the tornado plot of the subgroup analyses, and this is the least square mean difference between liprotamase and placebo.

There were eight different subgroups represented here, U.S. and non-U.S. sites, age, gender, and acid suppression, as you can see. The point estimates all favor liprotamase and there are some differences in terms of where those point estimates are. That, in our opinion, is not

surprising given the number of subgroups analyses that are represented here.

Did that address your question?

DR. SHIH: Yes, yes. I would like to have FDA address their conclusion of inconsistency here, that you view that they are not consistent. And I want to remind the people here, in a biostatistician's way, that you see the confidence interval overlap. That will give you a deception that they overlap, so they are not different.

However, the wide confidence interval means there is much uncertainty there because there is wide confidence there. So the side confidence interval was due to the small sample size. So don't get confused with the overlapping in applying consistency, because they are small sample size. The confidence interval is wide because they are uncertain. So that's why they overlap.

We are facing the same dataset. The company says they are consistent, the FDA says they are not consistent.

DR. RAJPAL: Can somebody put slide 43 from

our presentation? So if you look at the overall population, the 12 to 16 age group, it looks like they had a lower difference in the change in CFA, two compared to the other age groups.

So I think in the sponsor's presentation, they had used a 7-to-20-year age category and then 20 and above, whereas this is the age category we've used. And looking at it by country, on the next slide, there is the U.S. of 17 versus non-U.S. of five, and that holds also for the CFA less than 40 subgroup.

Go to the next slide. This one, the overall, they looked similar with acid suppression or not. But in the CFA less than 40, even though the numbers are small, it looked like there was higher difference in the on acid suppression versus not on acid suppression.

DR. BRETTMAN: I'd like to respond to that, please. If you could go back to your slide 43.

One other difference between the liprotamase studies and the porcine studies is liprotamase was a parallel group study. So the placebo is being

subtracted from the liprotamase effect. In a crossover study, that doesn't happen.

If you look in the overall -- and I would submit to you, you go into smaller groups, the Ns get too small to really draw any meaningful conclusions. But in the overall group, 7 to 11, in the liprotamase group, the difference was roughly 8 percent, roughly 8 percent in the 12 to 16 group, and 13.8 percent in the 17 to 44 age group.

Within this group are also included a substantial number of Eastern European and non-U.S. subjects that are nutritionally more compromised. So, again, it represents a very nutritionally compromised spectrum of subjects.

The liprotamase intra-treatment values are more comparable to a crossover type of design, and the placebo, if you'll notice, is the major reason for the difference there.

DR. RAUFMAN: Dr. Mulberg?

DR. MULBERG: Yes. Can I ask a question of the applicant?

DR. RAUFMAN: Sure, please.

DR. MULBERG: Thank you. Could you just elaborate on your comment that the nutritional differences in the Eastern European subjects contributes to a short-term assessment of CFA quantitation in which the trial was controlled supposedly the same in the U.S. and the ex-U.S. sites?

DR. BRETTMAN: Yes. So I cannot explain why there was a difference. There was a difference, you're absolutely correct. The populations, as you can see, are quite different and there may be an explanation in there, but I would be misleading you if I told you I knew exactly the answer.

However, I think the FDA is well familiar with what sometimes happens in international trials. So I don't think this is an unusual observation.

DR. RAUFMAN: Dr. Hubbard?

DR. R. HUBBARD: Thank you. I have a couple questions for not really the sponsors, but for Drs. Durie and Borowitz as clinicians.

If this product were available, how would

you use it? How would you recommend patients to be treated with it? Which patients would be put on the drug?

Would you say not using it in Eastern Europe or not using it in nutritionally compromised patients? As a clinician, what would you offer as advice to other clinicians on where to use this drug in the therapeutic armamentarium?

DR. BRETTMAN: Dr. Borowitz?

DR. BOROWITZ: So now I am speaking as a clinician and not as principal investigator for this study. If liprotamase were approved, it would be part -- it would be an option. I think if you say of the patients that I actively care for, in whom would I consider using this therapy, I would think about my teenagers. Teenagers are sick and tired of taking drugs, and that's a period of time where adherence is a real struggle. I would tell my patients put a few capsules in your cell phone case and text me if you're having trouble.

I would think about selected younger patients. Some of them have difficulty swallowing

a lot of capsules, drink a lot of fluid to try to get it down, and kind of suppress their appetite or, as has been stated before, are just incredibly embarrassed in front of their kids when they're taking lots of pills.

I would consider this option with their family, again, giving them the advice that this is a totally different product. I think the risk has been outlined and I believe it's real. We need to get a strong message across.

This is a totally different product. There's a limit. This is different. This isn't something where you just increase the number of pills.

I would say to adults who have been living with CF their whole life long, here is another option that's there for you. Adults with CF have seen over the course of their lifetime changes in therapy, things that have been sort of held as being really important.

I'll give you the example of nebulized tobramycin. People who started out with nebulized

tobramycin, that was the intravenous formulation, it works, but it wasn't a pure formulation.

So I would say to those adults, this is an option for you. And, again, in terms of risk mitigation, I would probably say you may have some abdominal symptoms initially during the transition period. We saw that early on in that first week or so. People have had exposure to porcine enzymes for their entire life. There is probably an effect on intestinal milieu, and there may be some changeover.

I can tell you that we saw that in some of the patients at my own site who then were very satisfied and, as someone else from the audience said, actually quite upset because of the financial reasons that there wasn't an extended program at the end of this.

That would be the way I would start using the drug, again, as an option. I certainly don't want to see porcine enzymes go away. Those are life-sustaining drugs, as well, but I'd like the option there.

DR. BRETTMAN: Dr. Durie?

DR. DURIE: First of all, I agree with everything that Dr. Borowitz said, but I just want to add a couple of other situations.

First of all, there is a subset of individuals with CF disease who clearly do not respond to pancreatic enzymes, and that is based on data. It's not based upon symptoms. It's based upon CFA and the fact that they may or may not be malnourished.

So it would be an opportunity to find out from those patients whether or not they would do better on this product. I'm not saying they will, but it's an option. It provides an opportunity to have another measure in order to do that.

The second point is -- and I recognize at this point, the committee is not considering approval for these indications at this meeting, but approval of this drug will inevitably lead to evaluation for younger infants.

Administration of the granules is very difficult in infants. And I'd just remind the

committee that infants are being diagnosed through newborn screening. So the pickup of patients with cystic fibrosis is happening in the newborn period in the U.S. in every single state. So this is a consideration down the road, where hopefully this will lead to evaluation in infants and allow easier administration.

DR. FREEDMAN: Perhaps I can just comment, just briefly, that although --

DR. RAUFMAN: Briefly is the operative term.

DR. FREEDMAN: Very briefly. So though we're focused on CF here, our center, probably one of the largest, we follow over 2,000 patients with chronic pancreatitis. And when you ask how are we going to use this, I can tell you that in many of my patients, that look like everyone sitting around in this room, that, frequently, the porcine pancreatic enzyme preparations are not that effective. So imagine that you can't sit here right now without having steatorrhea after today's lunch.

So I think when we think about how we use

this, in part, I don't want people to think we already have a prep that really works well in everyone.

DR. RAUFMAN: We're going to move on to some other questions. Ms. Sklar?

MS. SKLAR: Is there any data on adherence or lack thereof due to the perceived pill burden?

DR. BOROWITZ: The Modi study that I cited used MEMS caps, these electronic caps, so that each time you open up the pill bottle, something is registered. Subjects were given -- I was not a participant in the study. I just know the paper. But subjects were given multiple bottles for use at home, if they were living in two households, whatever it may be. And the adherence to the prescribed regimen for pancreatic enzymes was less than 50 percent.

DR. RAUFMAN: Dr. Hubbard?

DR. V. HUBBARD: I have a quick question and hopefully a quick answer. Is there any in vivo data as to where digestion is actually taking place?

You're making comparisons to some of the PEP preparations. And not only the impact of where digestion is taking place along the entire GI tract, not just the small intestine, but also the colon, and then the influence of pH on that.

DR. BRETTMAN: So the answer to your question is we do not have information from clinical studies, but we do have preclinical information which may be relevant to answering your question.

There is a porcine model of EPI that has been used for many years to evaluate porcine -- excuse me -- pancreatic enzyme replacement therapy. The CFA and triglyceride absorption data, please. One moment.

Slide on, please. I apologize for the delay. So this is the pig model, ligation of the accessory pancreatic ducts at the head of the pancreas are done and the pancreas involutes. It is not present after this procedure is done, and the pigs develop a syndrome quite similar to that of humans and dogs.

Next slide, please. This shows a comparison of liprotamase in terms of CFA to what is seen in healthy pigs on a high fat diet. There are actually two different doses of liprotamase indicated there. Let me just orient you to what's on this slide.

CFA percent is on the Y-axis and on the X-axis is the study group. So there's a control. A high dose of liprotamase, a low dose of liprotamase; in these doses, the low dose is relatively equivalent to the dose that we studied in 726 and the starting dose in 767. Then there's a washout period where CFA is measured again. CFA is also done in healthy pigs.

One point to make is that liprotamase compares -- it's similar to the CFA results that you see in healthy pigs. Now, your question specifically asked where in the gut is it active.

What this slide shows is that during the conduct of these studies, basically, a pharmacokinetic profile was established looking at the time of absorption of triglycerides, free fatty

acids, and non-esterified fatty acids. And across the X-axis here is time, and on the right-hand panel are healthy pigs, on the left-hand panel is liprotamase. And I think you can appreciate that there's a peak in the triglyceride at about two hours, which is comparable to where it is in the healthy pigs.

So that's the data that we have suggesting that liprotamase may be active earlier in the gut, but that's just based on this porcine data.

DR. RAUFMAN: Thank you. Dr. Hasler?

DR. HASLER: Two very quick questions. The first one relates to issues raised by both the sponsor and the patient and patient advocates concerning the capsule burden.

I'm just wondering if you could tell us how much of a reduction in numbers of pills or capsules you'll have. And the reason I ask that is just that, if I'm not mistaken, the currently available porcine products have -- the maximal strength ones are upwards of 20 to 24,000 lipase units per capsule and on slide number 9 from your

presentation, it's 32,000 units of lipase.

So are you really just substituting a big handful of pills for a small handful?

DR. BRETTMAN: So I think one thing to focus on are the number of units per gram of fat per day or the total number of units per day. So it is true that in the liprotamase product, there is more lipase by USP unit than, say, the 24,000 strength of Creon. So it's not a tremendous difference.

DR. BURSTYN: I think if I could add to it, one of the differences that I think needs to be recognized, the liprotamase are on small size 2 capsules, which hold about 200 mgs. In contrast, the porcine products are present in much larger capsule size or size double-zero. So in terms of the number of capsules, we're actually able to achieve these smaller capsules because we're using purified enzymes rather than having to rely on biological extracts.

DR. V. HUBBARD: The second question I have is also quick, which is directed to the clinicians

more than anything. A couple of people have mentioned that nutritionally challenged CF patients do sometimes require nocturnal tube feeds, and it's been proposed that these people be given enzymes.

Just to educate me, why would you not use an elemental tube formulation and not even worry about whether you have to give enzymes?

DR. DURIE: That's an excellent question. First of all, there's no such thing as a fully elemental tube feeding. They all contain substantial amounts of intact fat. Often, the elemental component of it is the protein.

So, again, we're trying to rely on improving fat assimilation. So it is an option and certainly, in some instances, people do feed individuals with those tube feedings without enzyme therapy.

But I think to optimize assimilation, you do have to administer enzymes, as well. And one of the problems with the existing products is if you put them in the bag -- you can either break them down or put them in the bag -- they just sit there.

They plug up the tube. And if you ingest them at the beginning of the evening, there's nothing left during the seven or eight-hour period of the feeding.

DR. BOROWITZ: Quickly. The other point is that the most concentrated two-calorie per cc formulas are not available as elemental formulas.

DR. RAUFMAN: Dr. Forsmark?

DR. FORSMARK: I had a question about adults with chronic pancreatitis. In many of the patients that are adult with that disease that have exocrine insufficiency will use 60 to 90,000 USP units per meal, and I haven't heard a lot about that group of patients and how you envision the dose or dose adjustment in adults with that disease.

DR. BRETTMAN: I'd ask Dr. Freedman.

DR. FREEDMAN: Dr. Forsmark, I think that's a great question, and I would view it just as we would dose a CF patient. Basically, if you're looking at someone who has almost no exocrine pancreatic function, I think the dosing would be the same whether it's total pancreatectomy, whether

it's chronic pancreatitis or exocrine failure, or whether it's CF with severe exocrine pancreatic insufficiency.

I think regardless of what the underlying etiology is, you're still going to dose, and dose not so much based on weigh and ager, but based on fat intake and what would control symptoms and maintain nutrition.

DR. RAUFMAN: Dr. Fogel, last question, brief.

DR. FOGEL: I'll actually pass right now.

DR. RAUFMAN: One brief, to come back to Dr. Shih.

DR. SHIH: When I asked the question, I had a second part that was not answered, and that was in your long-term study -- we're trying to focus on the issue of what percent of change – what change in the CFA would be constituted clinically meaningful?

So I want to establish a correlation between the CFA with your clinical endpoint, like BMI Z score. And the only chance that you had was in

your long-term study that you can measure both.

So I didn't see the presentation. I didn't see the data. So I'd ask the first question. Have you measured CFA in your long-term study or not?

DR. BRETTMAN: I apologize for not responding to that. So measuring CFA in 767 was really not considered possible for the reasons that the burden that these subjects are already under in participating in the trial, it was not felt that that could be done. However, I think we can address your question with the data that we have.

DR. SHIH: Yes. But you go over some, right?

DR. BRETTMAN: Yes, exactly. Exactly.

So if we could have this slide on, please. So what you can see on this slide is, remember, there were 88 subjects who were evaluated in the 726 study and they had -- all of the 88 had a baseline CFA done, and then there were 80 subjects who rolled over that ended up being randomized in the 726 study. Thirty-six of those received liprotamase during the randomized portion of 726.

Before I move on to that, we did a number of analyses looking at baseline CFA. So this is the off enzyme period, seeing whether that associated some way with nutritional outcome. We looked at the on-treatment CFA above and below a median to see if that correlated, and we looked at change from baseline CFA.

Of course, the on-treatment CFA and the change from baseline CFA could only be done in those subjects who were randomized to liprotamase, so the 36.

Next slide, please. So this shows above and below the median and the Ns do start to get small. And what you can see here is in blue are those subjects that had above the median change, and the median was 13.7, and below the median change, 13.7. And although the Ns are small, which leads to a little bit more noise in the lines, again, you see a similar pattern of nutritional maintenance.

DR. SHIH: That means no correlation?

DR. BRETTMAN: Well, I think the point that we think is important here is improving CFA is

important. The hurdle by which you need to improve the CFA to get clinical benefit clearly seems to be variable.

DR. SHIH: You could do a correlation study or you could do a regression, right?

DR. BRETTMAN: I would ask our -- Dr. Balser, do you want to address that? So could you repeat the question, please.

DR. SHIH: I want to see if CFA change resulted into greater BMI Z score a year later or not. So I wanted to see an analysis that relates these two, because you call it a surrogate endpoint.

So the first thing for a surrogate endpoint to be established is to establish the correlation. So have you done that correlation analysis? And then we can probably estimate a cutoff.

Okay. So correlation first.

DR. BALSER: Sure. This is John Balser, biostat consultant to Alnara. You certainly raise some good points. I think one of the things that Dr. Brettman mentioned is important to consider,

and that is the relatively small sample size that we're talking about here.

I understand your point about correlation, but it would be, I think, of more interest to see CFA change over time in a long-term sense, but really that's not feasible to do.

DR. SHIH: No, no, no. I'm not talking about CFA and long-term change. I'm talking about short-term change of CFA. You rolled over 88 patients. You do have data. Better than you don't have data, you don't have information. Eighty-eight patients is good enough.

DR. BRETTMAN: The problem is on the 88, we only have baseline CFA off enzyme. So let me just go over it again, because perhaps I wasn't clear.

Of those 88 subjects who rolled over, eight of those 88 were not randomized in 726 because their off-enzyme CFA in the 726 trial was greater than 80 percent. And so they were not considered to be sufficiently pancreatic insufficient to participate in that trial.

Eighty of the subjects were randomized in

726, and of those 80, 44 were randomized to placebo. So looking at the on-treatment CFA or the double-blind -- excuse me -- the change from baseline and the double-blind CFA perhaps in a placebo group wouldn't have been helpful.

So we have 36 subjects that were randomized to liprotamase in whom an intra-treatment change, that is, the change from their baseline off-enzyme CFA to their values on liprotamase, that was 36 subjects. And that's the data that you see here on the 36 subjects, N equals 18 above and below the median.

I might point out, it's interesting, we're talking about the small sample size here, these are 36 subjects. That is more subjects than in the pancreatic enzyme trials, and I think that's important.

Committee Discussion and Questions

DR. RAUFMAN: Let's move on to the questions. For the voting questions, we'll be using the electronic voting system. Each of you have there voting buttons on your microphone, yes,

no, and abstain.

Once we begin the vote, please press the button that corresponds to your vote. After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record.

Next, we will go around the room and each individual who voted will state their name and vote into the record, as well as the reason why they voted as they did.

So the first question for discussion and then vote, and I'll read them out loud: A, in the overall Study 726 population, is the observed difference in change in CFA between the liprotamase group, 11 percent, and the placebo group, 0.2 percent, of sufficient magnitude to be clinically meaningful?

Then part B of this, in the subgroup of patients with a baseline CFA less than 40 percent in Study 726, is the observed difference in change in CFA between the liprotamase group, 20 percent,

and the placebo group, 5 percent, of sufficient magnitude to be clinically meaningful?

So I'll open the discussion.

DR. SHIH: Is this a discussion or a vote?

DR. RAUFMAN: Well, we can discuss or we can vote. Does anybody want to discuss?

DR. SHIH: Yes, I would like to. I think, first of all, we have not established CFA change as a legitimate surrogate endpoint or not. Patients say that they do not measure it, they do not use it, and the company says that they haven't established the correlation, and FDA does not know either, the medical community.

I'm not a clinician, but I don't see CFA is an established surrogate endpoint. I just hate that we have data out there, that we have PEP studies, and we have the data, and we have data on this long-term study, but we are not analyzing the correlation, which is the first thing that you establish a surrogate endpoint.

That's my comment.

DR. RAUFMAN: Dr. Fogel?

DR. FOGEL: I have a question about clinically meaningful. Would that mean that that data would be considered adequate to show efficacy of the drug for clinical approval? Is that what clinically meaningful means?

DR. RAJPAL: I guess the other part for approval would be weighing in the risks.

DR. FOGEL: I understand that, but does clinically meaningful mean efficacy for clinical approval?

DR. RAJPAL: Yes.

DR. RAUFMAN: Dr. Van Hubbard first.

DR. V. HUBBARD: We've heard throughout the discussion today the variability of CFA in patients, per se. Do we have any idea as to the variability if this was repeated, any of these tests? What would be the level of variation?

DR. RAUFMAN: Can the sponsor address that question? That is, the reproducibility of the CFA.

DR. BRETTMAN: I believe we can.

Dr. Borowitz, would you like to address that?

DR. BOROWITZ: Let me orient you to this slide. Slide up. I showed you this before. This is the only data I know of that looks at the reliability of CFA as a test.

So along the X-axis you can see the CFA that was done at time number 1 in Study 726, and along the Y-axis you can see the CFA that was done at time number 2 for that subject, for these individuals who were assigned to placebo.

I want you to remember that these subjects were studied about a month apart, so they are clinically stable. And in this study, in the 726 study, not only did we do a CFA with our marker-to-marker stool collection in a CRC with a 100-gram fat diet that was used by a dietitian, with measured amounts afterwards, but the individuals ate the exact same foods.

So it's not just 100 grams of fat, the exact same foods. I think that's as precise as you can get in terms of methodology. And some subjects, in fact, had a pretty repeatable value, but not all of them did.

Again, this is placebo and placebo, some change by 30 percent.

DR. R. HUBBARD: Is there a correlation coefficient?

DR. BOROWITZ: Sorry, I'm blanking. And you can see the scatter around the mean. I think the other thing this shows you is here is the scatter around the mean. In every study that has ever been done, the range of CFA off of enzymes is from something in the teens that you think would be incompatible with life. I believe a CFA of 14 percent was our lowest in this study to something approaching 90 percent.

DR. RAUFMAN: Dr. Mulberg, to this point?

DR. MULBERG: Yes. Dr. Borowitz, per that slide, data, can you just expand, maybe, since it's not visible at least to my eye, on the individual change in values by percent, just in a general way?

Are we talking about 50 percent, 10 percent? What value is on T-1 and T-2 for each individual subject?

DR. BOROWITZ: I'm not going to be able to

give you all of those figures exactly, but I think you can use your eye.

Do I have a pointer?

DR. MULBERG: Only because to Dr. Hubbard's point, the correlation looks pretty strong, to my eyes. I'm curious to know if it's .7 or .8 or .6, but it's not .1, .2 or .3, right? It's good linearity there.

DR. BOROWITZ: Right. But on the other hand, the scatter is enormous and there are very significant outliers where the change can be by 20 or 30 percent.

DR. MULBERG: What I'm missing, unfortunately, and maybe others are getting it, is they're all red dots. I don't know what subject one did for both occasions.

DR. BOROWITZ: So a subject who might have had a CFA of around 50 percent at time one had a CFA that was in the teens around time two. That's what that dot is.

DR. MULBERG: Thank you.

DR. RAUFMAN: Dr. Forsmark?

DR. FORSMARK: I'm wrestling with the question a little bit, because we were presented data that was more than just CFA. We saw data on body mass or maintenance of body mass index. Shouldn't that be part of the question, as well, as to whether we think it's clinically meaningful that we're looking at all of the data that has been presented and not just that?

DR. RAJPAL: We ask that in the next question, number 2.

DR. RAUFMAN: That does come up in later questions. Dr. Krist?

DR. KRIST: I was going to pose, more to the group and the FDA, sort of a question about the vote. I see the buttons on my panel here and there's a yes and a no vote.

What I've actually heard is a decent amount of information that we don't know whether this has been linked as an appropriate surrogate and that we don't necessarily have it linked to outcomes, which the yes and no implies that I'm saying, yes, it is a good surrogate and that the 11 percent difference

is adequate, and the no is I'm saying it's not adequate for clinically meaningful.

But there is a middle, which is it hasn't been studied and we don't know the answer to what a clinically meaningful cutoff is. How does that get accounted for in the vote, and how are we supposed to think about that?

DR. BEITZ: The third option would be viewed as a no.

DR. RAUFMAN: Dr. Joad?

DR. JOAD: I just wanted to just reiterate that CFA does not appear to be an appropriate surrogate when what we really want to know are growth parameters and symptoms. So that's one point, for the reasons a lot of people have said already.

The second is a meaningful difference, to me, given, as a clinician, that porcine enzymes aren't that great -- and I would want anything that was approved to be at least as good as the porcine enzymes, and we don't have the comparison, but the best we have would say it's not. So there are two

reasons why I think it's a concern.

DR. RAUFMAN: Dr. Hubbard?

DR. V. HUBBARD: I just have a comment on the use of CFA as a surrogate. I think, personally, my bias is CFA is not necessarily a surrogate, in a sense, since the action of the drug is for digestion. The impact on weight, height, BMI, which may or may not adequately adjudge nutritional status, or is it something that is determined over the course of the long-term study, which there are too many other factors to really, I think, judge one item.

DR. RAUFMAN: Dr. Lowe?

DR. LOWE: I think I agree with everything that's said. We don't have the data to be able to be able to answer this question. I think all it tells us is that the preparation has some activity in vivo, because there was a change in the CFA.

The other data that we have, and I asked this question this morning, is we have the BMI data that has been presented in the slides, and there's also height and weight data that was presented on

the disk that was given to us. And there are some changes in those, but it's still unclear to me whether those changes are statistically significant.

It's also unclear to me whether they're driven by small subpopulations, as was suggested, for the drop in weight earlier on. It's perhaps that some of the weight gain was driven by small subpopulations or the height that you see was driven, because there are large standard deviations.

I'd like to understand that better, if somebody can help us, whether that data is meaningful, because that's really efficacy. And one could argue about what it really means for nutritional status, but, bottom line, we want the patients to gain weight and grow on these enzymes, and that's what people monitor.

DR. RAUFMAN: That's not a question. That was a comment.

Any additional discussion before we vote?

MS. SKLAR: I just would like -- you had

started with the efficacy and the clinically meaningful. Are there other points of clinically meaningful that you're looking for? Could you give me a specific definition of clinically meaningful?

DR. RAJPAL: Really, the first question that you had asked is the same as asking if there's efficacy.

MS. SKLAR: For A and B. Okay. So it's just hinging on efficacy, because you had just said something about risks.

DR. RAJPAL: That's my view, unless somebody wants to add anything.

DR. MULBERG: I think that we can add sufficient basis for approval, based upon what is deemed to be clinically relevant endpoints, which, in this case, in the cystic fibrosis patient, is growth and nutrition, as Dr. Lowe has intimated.

So what we have what we have as historical approvals and we have what we have regarding historical use of these types of products, albeit maybe a touch different on survival and on nutritional status. I think that's what we're

referring to.

DR. RAUFMAN: So let's move ahead with the voting. If there's no further discussion on this question, we will now begin the voting process.

Please press the button on your microphone that corresponds to your vote. We'll do question A first. We'll go around the table, then we'll do question B and go around the table in reverse.

[Voting.]

DR. RAUFMAN: So, for the record, the voting result on question 1-A is 1-yes, 10-no, 1-abstain. And we'll go around the table, starting with Dr. Krist.

DR. R. HUBBARD: I'm sorry. I didn't think my vote was supposed to count.

DR. RAUFMAN: That's the other Dr. Hubbard. That's been a confusion all day. But your vote didn't count.

So we'll start with Dr. Krist. And, basically, please state your name, what you voted, and why.

DR. KRIST: My name is Alex Krist. I voted

no, because of the question that I posed about uncertainty. I don't think we've seen any data to say what the clinically meaningful cutoff for a CFA would be.

DR. LIGHTDALE: My name is Jenifer Lightdale, and I also voted no for essentially the same reason.

DR. FOGEL: My name is Ron Fogel. I voted no, but my rationale is as follows. The first point is that CFA is a surrogate marker for what we're really interested in, as has been indicated. It's not a very good surrogate.

There are questions regarding the efficacy of the drug. We know that it's better than placebo, but we don't know if it's as good as the porcine products, given that those studies have not been done.

Having heard the public comments, it's clear there's a very important unmet need that has to be addressed. In my opinion, what is needed now is actually -- and I'm not sure how the FDA feels about this, but really an non-inferiority study to

see whether this drug is as good as the porcine products in fat absorption.

If it's as good as the porcine products, then I think the drug should be approved as just another alternative in therapy, because there is a very significant unmet need that's been identified in the public comments.

DR. FORSMARK: I'm Chris Forsmark, and I voted yes. I'm just very nervous about using CFA as an important clinical measure. And this improvement, although it's modest, was still associated with what I think is a more important outcome, and that's maintenance of weight. So I thought that based on that connection, I voted yes.

DR. LOWE: It's Mark Lowe, and I abstained, for really all of the reasons that were given before. I don't think we have the data to be able to answer that question in a meaningful and correct way. It's not a black or white question at this point.

MR. HAWKINS: Charles Hawkins, and I chose no. I recognize that there's a strong desire among

patients and caregivers to find something better for our needs, but the difference between what was available and what I was seeing today was just too different for me to vote any other way.

DR. SHIH: I voted no, because I believe there are data, they're just not analyzed properly or not analyzed at all. So I don't see an established correlation.

Regarding the cutoff, if there's no correlation, as the company says, then we should follow whatever they have agreed upon, what the FDA has requested, before the pivotal study started, which is 30 percent. That is not met here.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, for many of the reasons that were just stated. I was not convinced that the data showed meaningful efficacy for this agent, although it's obviously greatly needed.

DR. JOAD: I'm Jesse Joad, and I voted no, for the reasons I stated earlier. I'm particularly worried about children, who I thought had even a worse CFA change.

MS. SKLAR: I'm Jill Sklar. I voted -- I concur with Dr. Krist and Mr. Hawkins on their reasons for voting.

DR. V. HUBBARD: I'm Van Hubbard. I voted no, basically for the similar reasons that I think the data is insufficient at this time, although I recognize the need for alternative options. And I would say that I think that there is some promising information that was provided.

DR. HASLER: Bill Hasler. I voted no, for pretty much the same reasons as everybody else. I do want to congratulate the sponsor for really putting the effort to put on a very nice trial, which I think is far higher in quality than any of the porcine products which are out there.

I don't know if 11 percent is inferior to 40 or 50 percent, but I know that when I take care of chronic pancreatitis patients and I see such a modest improvement in fecal fat with a porcine product, I consider that an inadequate response.

DR. RAUFMAN: Thank you. In summary, the majority of the committee voted no based on what

was perceived as limited efficacy of liprotamase, but several members voiced the opinion, which I share, that a new approach to treating patients with cystic fibrosis and pancreatic insufficiency in general is needed.

So let's move ahead with a vote on part B, and I'll read this aloud. In the subgroup of patients with a baseline CFA less than 40 percent in Study 726, is the observed difference in change in CFA between the liprotamase group, 20 percent, and the placebo group, 5 percent, of sufficient magnitude to be clinically meaningful?

Please, go ahead and vote.

[Voting.]

DR. RAUFMAN: And the outcome was not different than before. Again, the voting result on question 1-B, 1-yes, 10-no, 1-abstain. And we'll go in reverse order, starting with Dr. Hasler.

DR. HASLER: Bill Hasler. My reason for voting no is the same as what I did for 1-A.

DR. V. HUBBARD: Van Hubbard, and I voted no, again, for the same reason. I think there's

insufficient information. And for somebody that has less than 40 percent to even increase 15 percent, that, by and large, would still be an unsatisfactory result.

MS. SKLAR: I'm Jill Sklar. I voted for the same reason I did in 1-A.

DR. JOAD: Jesse Joad. I voted no, for the same reasons.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, same reasons regarding lack of sufficient efficacy data.

DR. SHIH: Ditto here. Same reason as 1-A. I voted no.

MR. HAWKINS: Charles Hawkins. I also voted no, for the same reasons I stated before.

DR. LOWE: It's Mark Lowe. I abstained again to be consistent, because it's the same issues that we have with 1-A. I don't think that we were presented data with proper analysis to be able to answer that question in a fair way.

DR. FORSMARK: Chris Forsmark. For the same reasoning as the first time around, I voted yes.

DR. FOGEL: Ron Fogel. I voted no, for the same reasons.

DR. LIGHTDALE: Jenifer Lightdale. I voted no, for the same reasons, but also want to echo the same sentiments that clearly there's a need for new drugs.

DR. KRIST: Alex Krist. I voted no, for the same reasons, and I'll say the same thing that Jenifer did, as well, that there seems to be some value with different types of products here.

DR. RAUFMAN: So, again, in summary, very similar to my summary of part A, that the majority of the committee voted no on this question, not convinced of the overall efficacy of liprotamase relative to current therapy, but, again, noting need for additional approaches to treating these diseases.

We can go on to the next question. So let me read the question. We can then have some discussion. Do the results of Study 726 and the exploratory analyses of data from Study 767, including comparisons to CFF registry data,

constitute substantial evidence of the efficacy of liprotamase for the treatment of patients with exocrine pancreatic insufficiency due to CF, EPI due to CF in children less than 7 years of age, EPI due to CF in children greater than or equal to 7 years of age?

Any comments, discussion? Mr. Hawkins?

MR. HAWKINS: Are we assuming that A is for adults or for the entire CF population?

DR. RAJPAL: That's for the entire population.

DR. RAUFMAN: I agree, it is the entire population and it's broken down in B and C.

Dr. Hubbard?

DR. V. HUBBARD: Is there any clarification you can provide as to the true difference between this question and question 1?

DR. RAJPAL: Well, in question 1, we had said based on the Study 726, and here we're asking you to also consider the exploratory 767 long-term study data. And we also, at the same time, want to ask the question about the age.

DR. RAUFMAN: Ms. Sklar?

MS. SKLAR: Is there a reason why you didn't ask about CF patients over the age of 17?

DR. RAJPAL: Over 17?

MS. SKLAR: Well, one thing that really struck me in some of these things, when you looked at the BMI for all of this and the children were the ones, below 17, who seemed to be the ones who lagged in growth, and, of course, 17. Then you had the chronic pancreatitis patients and the pancreatectomy patients who were in the other studies, and they didn't seem to lose any BMI, which seemed to be a significant thing. They seemed to get some benefit out of it, but, of course, the issue was no loss in BMI.

So I think that's one thing that I've been thinking about. Was there any thought of prescribing this for patients who were over the age of 17 at all?

I know that was probably not included in these two studies, but that would be one thing that I would think would be interesting to consider.

DR. RAJPAL: The idea behind these questions was that there were no patients enrolled in either 726 or 767 that were less than 7 years. I think if you go to the last question at the end, it does ask you to consider --

MS. SKLAR: Greater than 7.

DR. RAJPAL: When you get to the final question about if you specify whether your answer is limited by particular subpopulations defined by age, because the issue you're raising is more in the overall risk-benefit, and this is really just looking at efficacy.

MS. SKLAR: At the specifics. Okay.

DR. RAJPAL: This is looking at efficacy based on the fact that these are the only ages of patients that were in the study.

DR. RAUFMAN: Any additional comments, discussion before we go ahead and vote?

[No response.]

DR. RAUFMAN: Okay. So the first vote is on A, exocrine pancreatic insufficiency due to CF, yes, no, or abstain.

[Voting.]

DR. RAUFMAN: A little different. So the voting results for question number 2-A, we have 3-yes, 9-no, and no abstentions. And, again, we'll start with Dr. Krist and go around that way.

DR. KRIST: I'm Alex Krist, and I voted no for this. And I need to say that I wanted to vote yes for this. The weight data for Study 767 over a year looked encouraging to me. But if, logically, on the first one, we're saying CFA is not an adequate -- or if we don't know the cutoff of it as a surrogate marker, Study 726 is our randomized controlled trial, and 767 doesn't have a comparison or a control group to really be able to assess whether that maintenance is appropriate and such.

So I think the big reason I voted no was because of the lack of a comparison with 767.

DR. LIGHTDALE: I'm Jenifer Lightdale. I voted yes, and I did it, actually, also, hesitating. This is not an easy vote. But I do think that there's been compelling evidence that CFA is active. It's showing some activity of drug,

and here there is clear statistical evidence that the drug is active when placebo isn't overall, at least if you look at the whole study of 726.

Then I think the 767 study really does show long-term that weight is maintained. So I just went with basic is the drug efficacious, and the answer is it's working, it's doing something. Is it doing enough I think will be an ultimate question.

DR. FOGEL: Ron Fogel. I wanted to vote yes, but I voted no, because, unfortunately, the data doesn't support the indication. The data from 767 I find hard to interpret without a control group.

DR. FORSMARK: Chris Forsmark. I voted yes again. I think this question explicitly included the results of the long-term study, which I was using implicitly in my answer to the previous questions. So still yes.

DR. LOWE: It's Mark Lowe. I voted yes to this, using that the 5th percentile was substantial evidence. I think, to me, the data showing that

the patients seemed to at least maintain weight, perhaps gain weight and gain height over the course of a year is reasonably compelling, and they did as well as patients in the CFF registry.

I recognize the issues raised by the FDA regarding problems with that comparison, but I also think if we're going to invoke historical data on the 30 percent CFA, I think the historical data would tell us that patients with CF off of active enzymes do not gain weight and would not grow well.

MR. HAWKINS: Charles Hawkins. I voted no. I think if the question was whether I could agree with approving it for adults, I would have said yes. But it seems like it's too risky to try in children at this point.

DR. SHIH: I voted no. I would contemplate this question versus the question 1. I think this question is really asking is the 767 -- add to the 726 to establish substantial evidence, and I emphasize the word "substantial evidence" there.

That's why I said no, because I don't think the evidence is substantial, for two reasons. One,

for the design, the study is not a well controlled study, which, when you ask, substantial evidence comes from a well controlled study.

For the BMI Z score, maintenance, I commented earlier that I don't think the last observation carried forward, analysis is an adequate analysis. I expect that we will do some analysis more than last observation carried forward in the presence of 30 percent of early withdrawal of patients. And then we didn't see the analysis show that the BMI Z score returned to the baseline after a year. So I voted no.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, because although I think there was some evidence, it didn't meet the bar of substantial evidence.

DR. JOAD: I'm Jesse Joad. I voted no. I felt like there needed to be a comparator group, and I didn't think the CF registry was adequate. There are just too many differences between being in the study and just being in a registry that could explain similarities or differences, and a

true randomized control trial really needed to have been done.

MS. SKLAR: I'm Jill Sklar. I voted no, for the same reason, in part, with Mr. Hawkins. I believe that if this was something that was for adult CF patients, that would be something that I could agree with. But if you're including the entire body, including children, whose BMI is such a challenge, I can't agree with that. And I also agree with the comparator.

DR. V. HUBBARD: Van Hubbard. I voted no, mostly because I equated efficacy with having some type of clinical significance, and I'm trying to be consistent in the way I'm looking at the data. And I do think it's insufficient in that sense.

The addition of Study 767 in terms of looking at weight and then some of the other parameters, I think there are too many other factors that go into the determination of those observations to be able to ascribe it to this particular growth.

DR. HASLER: Bill Hasler. I voted no. If

there had been a fourth button, I would have pushed maybe, because I do find the BMI data to be more compelling than the CFA data.

Nevertheless, if you do follow these people over a year during the conduct of a formal open label trial, I would have expected that the compliance with enzyme intake over that year would have been higher than before study entry when they were just in the general population. And I would have expected them, for a truly effective drug, to gain weight.

DR. RAUFMAN: So in summary of the voting on question 2-A, the majority voted no, although a strong minority voted yes, saying that there was evidence of efficacy. Those voting no felt that it was not substantial evidence and that there were issues with the control group in one of the studies.

So we'll go ahead and vote on B, which is -- I'll just read the part B, exocrine pancreatic insufficiency due to CF in children less than age 7 years. Yes, no or abstain.

[Voting.]

DR. RAUFMAN: So for question 2-B, there was a unanimous no. There were no yes votes, 12 no votes, and no abstentions.

I guess we'll start with Dr. Hasler.

DR. HASLER: Bill Hasler. I voted no, for the same reasons as last time, plus the fact that they didn't study the drug in people that young.

DR. V. HUBBARD: Van Hubbard. I voted no, for the same reasons.

MS. SKLAR: Jill Sklar. I voted no, for the same reasons.

DR. JOAD: Jesse Joad. I voted no, for the same reasons.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, for the same reasons.

DR. SHIH: And I voted no. Last time I said that there's no substantial evidence. This time, there's no evidence at all, and there's no data there. And, plus, if you look at the change, the delta in CFA, actually, it is less in 7 to 20 years old than those greater than 20 years old.

So if you're looking for trend, the trend is going to the opposite direction.

DR. HAWKINS: Charles Hawkins. I voted no, for similar reasons to what I said before.

DR. LOWE: Mark Lowe. I voted no, for the simple reason there was no data.

DR. FORSMARK: Chris Forsmark. I voted no because there was no data, and I was a little concerned about whether the idea of dissolving it in liquids or in the feed had been sufficiently studied in the way that it might be used in those very young kids.

DR. FOGEL: Ron Fogel. I voted no, because there's no data.

DR. LIGHTDALE: Jenifer Lightdale. I voted no, because there is no data; and, also, I respected, when I read the whole question, that they had pulled out this very young age group, and I do think there are concerns.

DR. KRIST: Alex Krist. I voted no, because there's no data. I think the value of this medicine in the younger population is that they'll

take it differently, and I think we need to evaluate the effects of that and make sure that it still maintains its benefits.

DR. RAUFMAN: So in summary of the voting on question 2-B, there was a unanimous no from the committee, based primarily on lack of evidence and then some concerns about the use of the preparations in applesauce or other forms that require additional study.

So we'll go on to question 2-C, and, again, we're voting now. I won't read the entire question, but on exocrine pancreatic insufficiency due to CF in children greater than or equal to 7 years of age. Yes, no or abstain.

[Voting.]

DR. RAUFMAN: And the results for question 2-C, 1-yes, 11-no, no abstentions. We'll start with Dr. Krist.

DR. KRIST: Alex Krist. I voted no, for the same reason I did with 2-A.

DR. LIGHTDALE: Jenifer Lightdale. I voted no, for the same reason I voted no in B, the second

part of my reason, which is I really did read that A is different from C in this question. And I'm not sure I'm comfortable the evidence is there, even efficacious evidence is there for the use of this drug. Exocrine pancreatic insufficiency in kids, period.

DR. FOGEL: I voted no because of concerns regarding the efficacy of the drug. We just don't have data for comparison.

DR. FORSMARK: Chris Forsmark. I voted yes, for the reasons I had mentioned earlier. I think we do have data at least in the 7 and above in this study.

DR. LOWE: Mark Lowe. I voted no, largely based on the subgroup analysis by age done by the FDA, where the change in the CFA was really all over the place and particularly in the 7 to 16 age group. And we don't have breakdowns I could find on things like weight gain and height gain and BMI in the age groups.

MR. HAWKINS: Charles Hawkins. I voted no, for similar reasons to what I said in 2-A.

DR. SHIH: I voted no, for the same reason as 2-A.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, because I just didn't feel there was substantial evidence of efficacy.

DR. JOAD: Jesse Joad. I voted no, for the same reasons as both the previous.

MS. SKLAR: Jill Sklar. I voted no, for the same reasons in 2-A.

DR. V. HUBBARD: Van Hubbard. I voted no, for the similar reasons.

DR. HASLER: Bill Hasler. I voted no, for the same reason as 2-A.

DR. RAUFMAN: So to summarize on question 2-C, the majority of the committee members voted no, based primarily on what was felt to be insufficient substantial evidence of efficacy.

I'll ask the FDA if we can skip question 3 based on the previous votes or do you need a vote on that?

[Pause.]

DR. BEITZ: Okay. We're counting three

yeses from question 2. So if the folks who voted yes in question 2 would like to comment on 3, we would make a note of that. Thanks.

DR. RAUFMAN: Dr. Forsmark?

DR. FORSMARK: Yes, but I think I would give them the same consideration that we give the other manufacturers, that if we approve it for CF, we approve it for the others, as well, based on the same data.

DR. RAUFMAN: I don't remember who else -- Dr. Lowe, did you vote yes?

DR. LOWE: I voted yes on 2-A and then consistently no on the other two. I think I would agree with Dr. Forsmark's explanation and that if it was granted to the PEPs, that it probably is granted to this. I don't think that the pathophysiology of the pancreatic insufficiency is significantly different. There are other intestinal differences.

DR. RAUFMAN: I think Dr. Lightdale was the third yes.

DR. LIGHTDALE: Yes. I was the third yes.

I will vote yes, as well, based on what Mark just said.

DR. RAUFMAN: Okay. So let's move on to question 4, please. Are there additional efficacy studies that should be obtained prior to approving liprotamase for exocrine pancreatic insufficiency? If yes, please describe the design of the studies, for example, placebo control, active control or dose ranging, including selection of endpoints, for example, change in CFA or clinical outcomes such as growth parameters, height, weight, and body mass index.

So I think we could go ahead and vote and then everybody can discuss it as we go around the room.

So are there additional efficacy studies that should be obtained prior to approving liprotamase for exocrine pancreatic insufficiency? Yes, no or abstain.

[Voting.]

DR. RAUFMAN: So on question number 4, there are 11-yeses, 1-no, and no abstentions. I guess

we'll start with Dr. Hasler.

DR. HASLER: Bill Hasler. I voted yes. I think that this is conceptually an exciting drug, and I would like to see more work done on it. I think studies which need to be done would include a long-term study of at least a year's duration comparing liprotamase to a unit-per-unit dose of a porcine enzyme preparation.

I think that that would not only tell us if the two kinds of enzymes are similar, but it would also validate CFA as an endpoint. I might want to switch to some of the anthropomorphic type parameters, such as BMI or weight, as the primary outcome and I would even consider throwing in blood tests to look for other nutritional parameters, including prealbumin and various vitamin and mineral tests to see if their nutrition truly is improved.

DR. V. HUBBARD: This is Van Hubbard, and I voted yes. I think that, again, there are promising observations that have been made with this drug. I think there are definitely patients

that would use this drug preferably over other available medications at the present time.

I think we need to have additional studies in which, one, we do observe the location of digestion along the GI tract. I would also like to have a little bit more dosing type of studies. I think the fixed dose approach needs to be complemented with other studies that adjust for intake.

I think if you're going to adjudge long-term impact on other parameters, that you need, also, to consider looking at CFA on customary diet. I know that raises its own problems, but if you're going to judge what is happening long-term, you also have to have some information as to what is taking place long-term.

MS. SKLAR: No, but I'm going to explain why. No, I said, for the adult population. I do think that there is a definite need for something out there that is an alternative to the porcine products. For those individuals, for example, for CF who have this, or people who have chronic

pancreatitis, or people who have had a pancreatectomy, I think in those patients, I do think we should probably continue to study them, but I think it would be okay to do it for those patients.

For the younger patients, I think there needs to be more, so yes for those. I went back and forth several times. For those individuals, I would want more of a study, more of the BMI, more of the longer range of what happens, because you saw that initial dip, but then it ended at a year, and you didn't see what happened years and years down the road with the 8-year-old who kept taking it.

So what would be what I would want to know.

DR. JOAD: Yes. I voted yes, and I feel like we really don't know how this compares with porcine enzymes. And so I would like a double-blind, randomized, controlled trial looking at real clinical parameters as endpoints, like height, weight, BMI; probably the secondary endpoints, including symptoms that were mentioned by our

speakers today of flatulence and frequency of stools and steatorrhea, that sort of thing.

Then I think two other studies that need to be done is the one that the sponsor said they would do in children under 2. Those children, 80 percent of them fail to thrive by the time you're 1 year of age, and they need enzymes and we need to know how to approach that with this, if it turns out this is a very good preparation.

Then a G-tube study needs to be done, because that is a huge need. And I think a comparison with what's being done now with porcine enzymes and the way that they think this will work could be a real niche for it and I think they should -- it would be great if they would show that.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes, for all of the reasons that were just mentioned. And I would add that in terms of looking at steatorrhea and so on, just general quality of life assays could also be performed in these studies.

I think somebody before raised the issue of whether these agents might have effects on the microbiome. Those are also things that could be analyzed in a well conducted study.

From what we heard at the public hearing session, there's a very definite need for new directions in the treatment of CF, and I would hate to not see advances in this area.

DR. SHIH: I voted yes. As I alluded earlier, the reason that 767 was not adequate evidence was because it's not well controlled. Therefore, if you do another study, it would be well controlled. I would suggest an active control, and you can do an equivalent study using the clinical endpoint as your primary BMI and FEV1, and you would measure the change of your CFA, as well, short-term, and so establish some kind of a correlation.

You would do a big favor to the medical community or scientific community to really figure out the real clinically meaningful change in the CFA. And I would do a stratified study that will

stratify by age, less than 7 and greater than 7 years old. And your younger population, you may be able to do a shorter-term than the slightly older patients, because their BMI may change faster or maintain their earlier, as your longitudinal study showed. They actually maintained after six months. So you don't have to do that long-term for those patients.

You may also want to consider not just including CF patients. You should include the chronic pancreatic, as well.

MR. HAWKINS: Charles Hawkins. I voted yes, mostly for what everyone else has said, but I also wanted to restate my opinion that if this was just being considered for an adult, I would have voted to approve the drug as is.

I think adults have better control or better experience at titrating their enzyme need based on their diet and how they feel, and I don't think the younger people, even with their parents' help, have that control yet. And so I think it would be better to try something with the adult-only

population at first before doing continuing studies on children.

DR. LOWE: Mark Lowe. I voted yes, for the reasons that have been thrown out. It's possible, as Dr. Shih said earlier, that a lot of the data on height, weight and body mass has been collected. Unfortunately, it wasn't collected with a well matched control group.

I suspect that because of the nature of this and the newness of this preparation, that a study that has a head-to-head control with current preparations is probably required using endpoints of nutritional assessment. I think the one thing that's come out of the discussions today is that the CFA is not likely useful.

DR. FORSMARK: I answered yes, I guess, because it seems at this point, based on the vote, that it's perhaps unlikely that this drug may be approved, and I think it would be a shame if we're just left with the same old porcine enzymes for our patients.

So I answered yes to suggest that if that's

the case, that the company do some studies that would satisfy this group that would make it available to patients. I guess the two things that have been raised as the major issues are some additional proof of efficacy, which I, again, would propose would be related to nutritional status or weight and some additional safety data to reassure us.

DR. FOGEL: Ron Fogel. I voted yes. In cystic fibrosis, the thinking seems to be that the porcine products improve fat absorption, which leads to weight gain, better BMI, which leads to better survival.

The only part for the porcine products that's been proven is the change in fat absorption. So I think a study that looks -- that is, as I said before, a non-inferiority study comparing porcine products with the new product for fat absorption would be the first study that should be done. That's a relatively easy study to do and relatively inexpensive.

I would like to see a second longer-term

study which looks at changes in weight over the period of a year, again, comparing the porcine product to this product. Obviously, we can't have a placebo-controlled study.

With regard to the other indications, the chronic pancreatitis, et cetera, I think there it's relatively easy to do a double-blind, placebo-controlled and/or crossover studies to get the data to prove that the drug is effective and that the indication would be needed.

I'm not sure that we should just use the cystic fibrosis data to say that the drug should be used for these other indications.

DR. LIGHTDALE: I'm Jenifer Lightdale. I voted yes. Certainly, there's clear evidence, as was heard in the testimony. But I also think, as a clinician and as a pediatric clinician, there are a number of things you could do to make drugs better for kids.

Actually, it was very nice to hear that this is a drug that's put emphasis on formulation, and being able to give it as a suspension to kids is

actually very important. And, actually, if they could make it work and get the right studies done to show it, to certainly be able to put it into G-tube feeds overnight would be humongous, would be wonderful.

In terms of how you design the study, I've heard a lot of different options and I agree with all of them. I think it would have to be -- at least one of the studies would have to be long-term, because I'd also agree with the clinical endpoint of growth in kids, if you're going to study kids, and maintaining BMI; if you're studying adults, is important.

I do think it would be important to go into the study a priori stratifying your study groups by age, nutritional status, and a number of the other risk factors that have been brought up today for possible reasons that the drug didn't look as efficacious as it might have.

DR. KRIST: I'm Alex Krist. I voted yes. I'd like to see an active control trial with outcomes that are growth parameters. And I'd like

to see the manufacturers of the porcine products participating in that, as well. We have historical data on benefits of their outcomes, and their main approval was around a surrogate that we're questioning.

DR. RAUFMAN: Thank you. So for question 4, there was a nearly unanimous vote of yes for additional studies. I think all the committee members were eloquent in describing their reasons for their vote, and I don't think it needs to be reiterated.

I think we can go on to question number 5. So there are two parts to this question. We'll vote on A first. Are there safety concerns associated with the use of liprotamase in exocrine pancreatic insufficiency, for example, distal intestinal obstruction syndrome, fibrosing colonopathy, other, that preclude approval; if yes, please describe.

So regarding safety concerns, yes, no or abstain.

[Voting.]

DR. RAUFMAN: Okay. So on question 5-A, regarding safety concerns with the use of liprotamase in exocrine pancreatic insufficiency, 6-yes, 4-no, 2-abstain. And we'll go around the room, starting with Dr. Krist.

DR. KRIST: I'm Alex Krist. I voted yes. It was a wishy-washy yes in the sense of I was also considering the safety concern of failure to grow. That's how it was framed at the beginning by the FDA as a potential safety concern.

I could see an issue with patients titrating their doses up. There seems to be a diminishing effect of increasing doses, potentially a ceiling effect, which could expose patients to take higher doses and increase their risk of intestinal obstruction or fibrosing colonopathy. But there wasn't really data that I saw that necessarily made me concerned about that from what was presented today.

DR. LIGHTDALE: I'm Jenifer Lightdale. I voted yes, actually, for the same reasons. Really, with the younger age groups, I think the safety

concern is poor growth.

But I also actually would point to -- and maybe this will come up in B, more of the liver function testing which needs to be thought about as you move forward.

DR. FOGEL: My name is Ron Fogel. I voted no. I don't think that there are safety concerns. I wasn't impressed with the safety data that would indicate that there's something that one would have to worry about. I think with appropriate attention to dosage, one should not have any problems.

DR. FORSMARK: I'm Chris Forsmark. I actually voted no, but I must have hit the wrong button, because it says yes. I'm sorry about that. Maybe my glasses slipped.

[Laughter.]

DR. FORSMARK: I felt the same as Ron. I though the DIOS and the elevated liver tests were more the background of cystic fibrosis and couldn't be laid at the feet of the enzyme.

DR. RAUFMAN: We'll correct the record and indicate that Dr. Forsmark voted no on question

5-A.

DR. LOWE: I took this question 5-A to mean with the data that was presented, and so I voted no, because I wasn't concerned with the adverse events that were described. I think they are within the background of the patient population.

MR. HAWKINS: Charles Hawkins. I voted no. The few cases of DIOS and elevated liver enzymes are stuff that I've been dealing with on the porcine products for a long time. So I didn't think it was any more than what I've seen among other friends.

DR. SHIH: I voted abstain, because I feel the study's sample size was limited and the exposure was limited, as well.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes, for similar reasons as Dr. Krist mentioned, concerns that if the drug wasn't efficacious, weight loss and growth retardation would be issues, and then possibly dose manipulations could result in other adverse events.

DR. JOAD: Jesse Joad. I voted no. None of

the data I saw today would have precluded me from approval of the drug if I thought it as effective. And I though the GI issues that they brought up were not safety concerns, but were really lack of efficacy concerns.

Of course, as always, I think there needs to be, if this is approved, Phase 4 studies where you look at what happens down the road with things like some of the things that have been mentioned.

Thank you.

MS. SKLAR: I'm Jill Sklar. I voted no -- I mean yes, and it had to do with the growth issue.

DR. V. HUBBARD: I'm Van Hubbard. I abstained on this question. I did not feel that there was anything definitive shown today to identify risks associated with this drug.

I do feel that, in its use, that other studies are needed at higher doses. It comes back to my question, I think that we need to know a little bit more about where this enzyme is active and whether there is any potential for the fibrosing colonopathy that was observed. What was

the actual cause and effect in those cases? I think that, obviously, the -- I think higher doses of any drug will be used, especially if you're trying to achieve above 80 percent coefficient fat absorption.

No data was presented to identify risk, but I think in its actual use, it still is a possibility.

DR. HASLER: Bill Hasler. I voted yes, primarily for reasons which are already described; namely, nutritional parameters, such as BMI. I suspect that some of the other AEs which were possibly associated may have related to this, such as the occasional episodes of heightened transaminases.

With respect to the fibrosing colonopathy, I think the data here is inadequate to address this. You'll really need extensive post-marketing surveillance to look for that. I do note, however, that the dosage that they've put into their pill of 32,500 units is in the same unit range, which was removed from the market back in the '90s when

fibrosing colonopathy was first described.

DR. V. HUBBARD: I'd just make an additional comment. I'm not sure, because of what we did learn when we observed this on a population of colonopathy, whether any clinical trial is actually going to show that information. I think it has to at least be on the radar screen.

DR. RAUFMAN: So in summary, on question 5-A, there was an even split of votes, 5-yes, 5-no, 2-abstentions. Those who voted no were satisfied that the safety data provided don't show a significant signal for concern. Those who voted yes, one of the concerns was that if the drug was less efficacious, so weight loss and growth retardation might be a concern. There was a concern that the Ns were too small in the studies and that there still might be some safety concerns that weren't yet apparent.

Then, finally, that if the drug was less efficacious and dosing was increased, that that might result in fibrosing colonopathy or other issues.

So we'll move on to question 5-B. Are there additional safety data or studies that should be obtained prior to approving liprotamase for exocrine pancreatic insufficiency? And we can take a vote and then people can describe, if they voted yes, what those additional data or studies should be.

So question 5-B, yes, no or abstain.

[Voting.]

DR. RAUFMAN: So for question 5-B, the voting results are 7-yes, 5-no, no abstentions. And we'll start with Dr. Hasler.

DR. HASLER: I voted yes, but I think that most of the information that we would get could be easily gleaned from a prolonged comparison trial of liprotamase versus a porcine product. And although this wouldn't influence approval of the drug, I think that since CF patients are followed so rigorously and closely in the registry and by clinicians, that this group, I think, would be amenable to very careful post-marketing surveillance to look for the more rare

complications.

DR. V. HUBBARD: This is Van Hubbard. I voted yes. I think that there needs to be additional studies looking at dosing, and then just the long-term study done with the higher doses just for observational purposes.

MS. SKLAR: Jill Sklar. The concern that I had was with growth, and the growth thing is something that I think if there were -- should it be approved for that. So that's how I read that question was if there are additional safety data or studies that should be obtained prior to approving liprotamase for EPI, I was thinking in CF for that particular one. And I don't think -- in the children at this point, it should be studied for a lot longer before it is approved.

For the other states, no, I didn't see that there were any major concerns, because the population sees some of these conditions all the time.

DR. JOAD: I voted yes. No. I voted no. I don't think there needs to be more studies. I'm

very much in favor of the efficacy comparator study. And if they would just follow the same things with a bigger N, that would satisfy me.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes, for the same reasons expounded by Drs. Hasler and Hubbard.

DR. SHIH: And I voted yes, but it can be the same study as we suggested or I suggested in question number 4 for the addition of an efficacy study. The safety is also measured there.

MR. HAWKINS: Charles Hawkins. I voted no, but I was looking at it more from the point of view of looking for adverse events versus the growth aspects and efficacy aspects, which I think do need to be looked at further.

DR. LOWE: Mark Lowe. I voted yes. I agree with some of the comments that are done, but I've got a little more specific concerns in that this preparation most likely does not contain phospholipase activity. It also doesn't contain an enzyme that will hydrolyze fat soluble vitamin esters, and it's unlikely to hydrolyze

galactolipids, although that's probably less important.

The reason that phospholipase activity may well be important is because humans maintain their choline homeostasis by recovering the choline from the phosphatidylcholine that is secreted in the bile, which is actually the biggest source of phospholipid in your duodenum.

There is some data, not great data, to suggest that choline deficiency may contribute to liver disease in CF patients. So I think that's something that would need to be followed both in another study and ongoing.

Also, the lack of ability to hydrolyze fat soluble vitamin esters could be an issue. I realize that they're going to be given a water soluble enzyme preparation, although it's not clear how well that works. And in some patient populations, particularly those with cholistasis, they're not absorbed very well.

So I think that fat soluble vitamin levels clearly need to be monitored as part of the

nutritional parameters in the other study.

Thank you.

DR. FORSMARK: Chris Forsmark. I voted no. As studies of enzyme therapy go, the ones we were presented today are larger than just about any I'm aware of. So I thought the patient population was quite substantial and sufficient to make judgments about safety.

DR. FOGEL: Ron Fogel. I voted no. I think that post-marketing studies will be needed. I think the adverse events are rare and they'll probably only show up when large numbers of patients are studied.

DR. LIGHTDALE: I'm Jenifer Lightdale. I voted yes, for the same reasons I voted yes in A. But I would also put in that in addition to safety data and studies, again, a definition of distal intestinal obstruction syndrome would be important, at least a study definition going in, especially if it's multicenter, KUB, et cetera, however you want to define it.

DR. KRIST: Alex Krist. I voted yes. I'd

like to see -- because I counted the failure to grow as part of the adverse events. So I think the efficacy studies would help me, and then the post-marketing studies for the rare events would also help me.

DR. RAUFMAN: So to summarize for question number 5-B, more people voted yes than no regarding needs for additional safety data. There were concerns raised about possible safety concerns with higher doses of liprotamase and, also, issues about the failure of this enzyme preparation to hydrolyze some important vitamins or other nutrients and that that required additional study.

So we'll move on to the last voting question, number 6-A. Based on currently available data, do the benefits outweigh the potential risks of liprotamase for the treatment of patients with exocrine pancreatic insufficiency? If yes, specify whether your answer is limited to a particular subpopulation defined by age or etiology of exocrine pancreatic insufficiency.

This is a little repetitive and I guess we

can go ahead and vote on it and then discuss.

[Voting.]

DR. RAUFMAN: For question 6-A, based on currently available data, do the benefits outweigh the potential risks of liprotamase for the treatment of patients with EPI? We have 4-yes, 7-no, and 1-abstain. And we'll start with Dr. Krist.

DR. KRIST: Alex Krist. I voted no. I heard that there's a need for this drug. I heard that there could be potential benefits for patients. And as we've talked here, I wasn't convinced that the efficacy data was adequate. And really what I would need to see is better efficacy data.

DR. LIGHTDALE: I'm Jenifer Lightdale. I voted yes, I believe, consistently with myself, because I also voted yes to 2-A. And if I was going to specify, I think in adults right now, there's efficacy of the drug to some extent and it's out there and the risks don't appear to outweigh those benefits.

DR. FOGEL: Ron Fogel. I voted no. Based

on the data that was presented, I don't think that there's any benefit, given that the risks are low, but there are some risks. I don't think the benefits outweigh the risks.

If the question was worded, "With the appropriate data, would the potential benefits outweigh the potential risks," I think the answer is yes. We just don't have the efficacy data to let me reach that conclusion.

DR. FORSMARK: I'm Chris Forsmark. I voted yes. Again, I would have liked to have seen even better efficacy data, but I felt overall, and particularly taking into account the comments from the public, that I thought the benefits outweigh the risks with this drug.

I would probably limit it to children above the age of 7 that have been studied and adults, not the younger kids.

DR. LOWE: Mark Lowe, and I voted no, which I realize is inconsistent with my yes vote on 2-A. And I think it's because it's not a -- we don't quite have enough data to be completely sure,

although I think the data in adults is probably stronger than the data in young kids and children, and that may be an appropriate group.

MR. HAWKINS: Charles Hawkins. I voted yes, but I would limit that to the adult population. And just speaking for myself, I probably would not take it without additional efficacy studies or proof that it's working at maintaining and improving nutritional condition.

DR. SHIH: I voted no, because as I alluded earlier, I don't see much substantial evidence of efficacy here. We don't have an established surrogate and we don't know what the cutoff was established. I think I really look forward to having a real clinical endpoint study to this.

DR. RAUFMAN: Jean-Pierre Raufman. I voted no, for the reasons just stated.

DR. JOAD: I'm Jesse Joad. I voted no, entirely due to my concern that the benefits haven't been shown adequately, and I would be very concerned if there were a drug -- if this were out there and available for people to use, given the

wonderful things of taking less number of capsules and being able to dissolve it in water, those are all such strong things that would make a patient want to use it. And if it's not as good as what we have, that would be a very big concern to me.

MS. SKLAR: Jill Sklar. I voted yes, with the caveat for the adult population.

DR. V. HUBBARD: Van Hubbard. I voted abstain, because I was in a quandary. I wanted to be consistent. I don't think that we have the data yet to definitively show the benefits. I think that the drug does have activity, and I also don't think that there's been any documented negative effects that can be ascribed to the drug itself.

I think the potential for benefits do outweigh the potential for negative side effects, but from the data we had, I left my vote as abstain.

DR. HASLER: Bill Hasler. I voted no. And although I don't think the drug has tremendous risks, I think that really there's been inadequate documentation of efficacy. And so I think the

ratio there is low.

DR. RAUFMAN: So, again, in summary of question 6-A, there were more nos than yeses. The nos were primarily based more on lack of substantial efficacy than they were on the potential risks. And for those who voted yes on this question, I think every one of the yes votes indicated that this was for people over the age of 7.

So perhaps we can go around the table one more time, starting with Dr. Hasler, to address the discussion point. If this product were approved -- I'll reword it -- are there any additional studies you would recommend post-approval?

DR. HASLER: I think primarily surveillance for very rare side effects would be important. You mentioned the issues of quality of life, and I think quality of life takes many forms.

One thing that I could see being done is since a lot of these people are school-aged kids or teenagers, are they able to improve their diet, and there's a number of very comprehensive food

questionnaires which can give very comprehensive assessments of intake.

I would love to see if a good enzyme preparation that's well tolerated could actually improve that aspect of quality of life.

DR. V. HUBBARD: This is Van Hubbard. I think post-marketing observations and analysis is needed, in general. Again, I think additional dosing studies and looking at the -- following-up on the preliminary observation of what appears to be a beneficial effect of pH alteration, whether that be with other pharmacological agents or just knowing the variability of patients in terms of the acid or the pH of the intestinal tract. That may offer some of the explanation for the variability and the differential response.

MS. SKLAR: I think a surveillance database, establishing one to look at the outcomes throughout a longer time, especially -- what I would be interested in would be the adverse events, the ones that were rare, the fibrosing colonopathy and the obstructions. That would be something I would want

to know in the longer term.

DR. JOAD: I agree that fibrosing colonopathy has to be looked at after it's approved. I would think the CF registry, in this case, would just make it much easier than usual to look at post-marketing efficacy and safety in many ways. So it would be great to delve into that database post-marketing.

DR. RAUFMAN: I agree with all those comments. And I'd also like to see some data on how the product is used; that is, how many capsules do people take when they start to titrate doses, as they inevitably will. So I think that would be of some interest, and it could be linked to any adverse events that were reported.

DR. SHIH: Let me just first say that I heard the Foundation of Cystic Fibrosis people and the patients out there who are suffering the disease and I really sympathize with them. However, this question is saying that if you believe this product should be approved, and I don't think so. I think that's premature.

I do not want patients to pay a lot of money for medicines that have not established their efficacy and risk their life, risk their health to potential risks of growth retardation. And so I believe the study -- that further data analysis should be done and further study should be done.

So I don't believe the product should be approved at this point. At least I want to see some additional analysis that I think is lacking there.

MR. HAWKINS: Charles Hawkins, and yes to pretty much everything that's been said so far.

DR. LOWE: Mark Lowe. I agree with most everything that's been said so far. I think it would be important for ongoing nutritional studies with time, because micronutrient deficiencies, for instance, may take more time to develop than you might see in a study period of even a year.

DR. FORSMARK: Chris Forsmark. Separate from sort of the usual post-marketing surveillance that's done for all drugs, I think some study of weight gain and growth over a prolonged period of

time would be terrifically interesting from a scientific point of view at least.

DR. FOGEL: Ron Fogel. I said yes. I think the studies that have been mentioned so far have all been excellent. The only area that I'd like to see investigated further is adult chronic pancreatitis, look at the effects of the drug on quality of life.

DR. LIGHTDALE: I agree with everything that's been said.

DR. KRIST: I agree with what's been said, as well.

DR. RAUFMAN: Are there any additional comments, questions from the FDA? Ms. Sklar?

MS. SKLAR: I always seem to close these things with patient education being very important and that if this does eventually get approved, making sure that the patients are educated and the physicians are educated to the appropriate usage of this in the most appropriate way, which would be a multichannel approach, in print and the Web.

Adjournment

DR. RAUFMAN: I want to thank everyone, FDA, sponsor, members of the committee, those in the audience, for an outstanding session. We're adjourned.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)